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Research Article

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Evaluation of the wound healing activity of twelve herbal and non-herbal remedies used in Sana'a-Yemen for the treatment of wounds and burns

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ABSTRACT

Wound healing is a complex process of integrated and overlapping phases resulting in the restoration of structural and functional integrity of injured tissues. Wounds and burn wounds represent a significant burden on the patients and health care professionals worldwide. There is still an obvious lack of suitable wound healing drugs since most of the available products can have some side effects and limitations. Traditional medicine has been practiced by the indigenous people of Yemen from antiquity until today. However, many of herbal and non-herbal products, used for wounds treatment, have not been the subject of any scientific investigation. Hence, the aim of this study was to document and scientifically evaluate the claimed wound healing efficiency of twelve herbal and non-herbal remedies (nine plants, one mineral (potassium alum), one marine product (cuttlefish bone) and one animal product (honey) used in Sana'a by indigenous people to treat wounds and burns. Searching electronic databases has indicated various experimental studies demonstrating four distinct pharmacological activities (anti-inflammatory, antioxidant, antimicrobial activities and promoting various phases of wound healing) displayed by the raw materials, extracts, chemical groups and some isolated compounds of the studied herbal and non-herbal remedies. According to the reviewed literature no serious side effects have been described for the remedies when applied topically. This study provides scientific data that support the wound healing efficiency of the studied remedies and thus lend some scientific justification for their traditional use in Sana'a for the treatment of wounds and burns. These herbal and non-herbal remedies can be considered as leads for future materials for wound healing and therefore further experimental and clinical studies are required to validate their effectiveness and safety.

KEYWORDS: Anti-inflammatory, antioxidant, antimicrobial, wound healing, herbal and non-herbal remedies, Yemen

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INTRODUCTION

Traditional medicine (TM) is widespread throughout the world and has been practiced for centuries. According to WHO [1], the use of TM has increased, and more countries are recognizing the role of traditional and complementary medicine in their national health systems. In Yemen, traditional medicine remains prevalent in rural areas and to some extent in urban areas. The wider acceptance of herbal medicine among Yemeni people is due to several reasons such as rich flora, better accessibility, poverty, low cost of herbal drugs, shortage of hospitals and health centers in remote areas, and lack of faith in modern medicine. Yemeni medicinal herbal and non-herbal materials have been used by indigenous people for the treatment of a number diseases such as infectious, parasitic, pulmonary (including tuberculosis), gastrointestinal, urogenital, ocular and skin diseases, including wounds and burns [2-6].

Wounds are major causes of physical disabilities. According to the wound healing society, wounds are physical injuries that result in an opening or breaking of the skin that causes disturbance in the normal skin anatomy and function [7]. Wounds represent a significant burden on the patients and health care professionals worldwide. They not only affect physical and mental health of millions of patients but also impose significant costs on them. Current estimates indicate that worldwide nearly 6 million people suffer from chronic wounds. Unhealed wounds constantly produce inflammatory mediators that produce pain and swelling at the wound site. Chronic wounds may even lead to sepsis with multiple organ failure or death of the patient [8]. According to the WHO's

International Classification of Diseases version 10 (ICD-10), burn injuries are classified by site of injury in chapter XIX as "burns and corrosions", (T20-T32) and in terms of aetiology they are classified as those caused by exposure to smoke, fire and flames (X00-X09), contact with heat and hot substances (X10-X19), exposure to electric current (W85-87), lightening (X33) and exposure to corrosive substances (X46-X49). Therefore, burns include scalds as wells as injuries caused by heat from electrical heating appliances, electricity, flame, friction, hot air and hot gases, hot objects, lightening and chemical burns (both external and internal corrosions from caustic chemicals). Radiation-related disorders of the skin and subcutaneous tissue and sunburn are not included in this classification of burns [9]. According to the depth, burn wounds are classified as first degree (superficial), second degree (partial thickness) and third degree (full thickness) [10]. Burns are a global public health problem, accounting for an estimated 180 000 deaths annually. The majority of these occur in low- and middle-income countries and almost two thirds occur in the African and South-East Asia regions [11].

Wound healing represents a dynamic and complicated process involving a series of co-ordinated events, including haemostasis, inflammation, proliferation, and tissue remodelling resulting in the repair of severed tissues and restore their structural and functional integrity [10,12]. Although several topical preparations are present on the market for management of wounds and burn-wounds, there is still an obvious lack of suitable drugs since most of the available products have antimicrobial activity rather than a wound healing effect. In addition, they can lead to probable negative effects on healing and even toxicity, as in the case of silver sulfadiazine on fibroblasts [10], neutropenia, methaemoglobinemia and renal toxicity [13,14]. Medicinal plants can act as wound healing agents because of their variety of different constituents like alkaloids, essential oils, flavonoids, tannins, terpenoids, saponins, fatty acids and phenolic compounds, which are potentially able to improve the healing process of wounds. Low cost, availability and fewer side effects are other advantages of herbal remedies [10]. More than 70% of wound healing pharma products are plant based, 20% are mineral based and the remaining contain animal products as their base material [7]. In recent times, focus on plant research has increased all over the world and a large body of evidence has been collected to show the immense potential of medicinal plants used in various traditional systems [7]. Hence, we conducted our work with the objectives to scientifically document and evaluate twelve herbal and non-herbal remedies used in the city of Sana'a (Yemen) for the treatment of wounds and burns. Consequently, we aimed to firstly contribute to preserving the indigenous knowledge of traditional medicine and save it from disappearing as well as secondly, to provide scientific justification for the use of these natural materials as wound healing agents. It is hoped that this study will encourage interest for further scientific investigations regarding the wound healing effectiveness and safety of the remedies's raw materials being used and their active constituents.

MATERIALS AND METHODS

Study Area

The study area is the city of Sana'a. This is the largest city in Yemen and the center of Sana'a Governorate. Sana'a has an area of 126 km^2 and a population of approximately 3,937,451 [15]. Detailed information about the vernacular names, uses, preparations and mode of administrations of the herbal and non-herbal remedies used in Sana'a for the treatment of wound and burn wounds were obtained by questioning the traditional medicine practitioners in their shops and practices.

Literature Review

Electronic databases of Leiden University library catalogue were searched for pharmacological activities demonstrated by *in vivo*, *in vitro*, or clinical studies and their possible mechanisms of action related to wound healing efficacy as well as the side effects for each of the herbal and non-herbal remedies involved in this study.

RESULTS AND DISCUSSION

Skin disorders, especially wounds and burn wounds, represent a global public health problem as their treatment is very costly and time-consuming. Moreover, the treatment of non-healing wounds, such as diabetic foot ulcers, has always been a challenge. Silver sulfadiazine, an antibacterial agent, introduced as the gold standard in topical burn treatment was found to cause side effects such as delaying the wound healing process [16,17], and toxicity to host cells [18]. Moreover, silver sulfadiazine has systemic complications such as neutropenia, methemoglobinemia and renal toxicity [13,14]. The silver released from its commercial products was reported to cause transient leukopenia secondary to bone marrow suppression [17] and cytotoxic effects on both keratinocytes and fibroblasts [19]. So, there is a need for better and more cost-effective alternatives for the treatment of wounds and burns that are devoid of serious side effects. Plants and other natural products that have been used in traditional medicine for a long time represent a valuable source to be explored for a variety of pharmacologically active secondary metabolites that may help in the treatment of diseases. Based on data collected by questioning the traditional medicine practitioners, we documented twelve herbal and non-herbal remedies used in Sana'a for the treatment of wounds and burns. The herbal materials were identified at the Agriculture Research Center in Dhamar-Yemen. Table 1 presents the ethnobotanical data of the herbal and non-herbal remedies used in Sana'a for the treatment of wounds and burns.

The herbal and non-herbal remedies used in Sana'a for the treatment of wounds and burns includes nine herbs from various families (Asphodelaceae, Compositae, Fabaceae, Lamiaceae, Linaceae, Lythraceae, Myrtaceae, Polygonaceae), one mineral (potassium alum), one marine product (cuttlefish bone) and one animal product (honey). They are prepared in the forms of infusion and decoction for rinsing wounds or used topically

Table 1: Ethnobotanical data of studied herbal and non-herbal remedies used in Sana'a for wounds and burns healing.

Scientific name /Family	Vernacular name	Part used	Preparation and mode of administration[1]
Aloe vera (L.) Burm. f. (synonym with the Yemeni variety, *Aloe vera* var. *officinalis* (Forssk.) Baker)/ Asphodelaceae	Sabir	Leaves	1- Topical application of crushed leaves on wounds and burn wounds. 2- Topical application of crushed leaves mixed with fat on burn wounds.
Astragalus gummifer / Labill., and other *Astragalus* species, Fabaceae	Al-Kathira	Gum from the trunk and branche (Tragacanth gum)	Topical application of powdered gum on burn wounds.
Chamomilla recutita (L.) Rauschert / Compsitae	Baboonig	Flowers	Rinsing wounds with an infusion or a decoction of the flowers.
Cuttlefish bone/ Sepiidae	Lesan Al-baher	An internal shell	Topical application of powdered cuttlebone on burn wounds.
Honey	Assal	Honey	Topical application of definite amount of honey on wounds and burn wounds.
Linum usitatissimum L./Linaceae	Al-Katan	Seeds oil	Topical application of seed oil mixed with egg white on burn wounds.
Meriandra bengalensis (J.Koenig ex Roxb.) Benth/ Lamiaceae	Dhru	Leaves	Rinsing burn wounds with an infusion or a decoction of the leaves.
Myrtus communis L./Myrtaceae	Hadas	Leaves	Topical application of crushed leaves on wounds.
Potassium aluminum sulfate dodecahydrate (potassium alum)	Shab Al-Fuad	Potassium aluminum sulfate	Topical application of powdered material on wounds.
Punica granatum L./Lythraceae	Romaan	Pericarp (fruit peels)	1- Topical application of crushed peels on burn wounds. 2- Topical application of crushed peels mixed with fat on burn wounds.
Rumex nervosus Vahl/ Polygonaceae	Athrub	Leaves	Topical application of crushed leaves mixed with fat on the wounds and burn wounds.
Thymus laevigatus Vahl (a synonym of *Thymus serpyllum* L.)/ Lamiaceae	Zater	Leaves	Rinsing wounds with an infusion or a decoction of the leaves.

[1]= The methods used by the local herbal healer in Sana'a

either as crushed or powdered materials or as a mixture with fat, or egg white (Table 1). These remedies (Table 1) can be grouped into 1- remedies (such as *Aloe vera* leaves, honey and *Rumex nervosus* leaves) used for the healing of both wounds and burns indicating the possibility of a broad spectrum of their pharmacological effectiveness; and, 2- those remedies used either for burn healing only (such as tragacanth gum, cuttlefish bone, *Linum usitatissimum* seeds, *Meriandra bengalensis* leaves and *Punica granatum* fruit peels) or for wound healing only (such as *Chamomilla recutita* flowers, *Myrtus communis* leaves, potassium alum and *Thymus laevigatus* leaves) suggesting a possible selectivity of their effectiveness. It is noteworthy to mention that local herbal healers did not specify the depth of burn wounds they treated.

Searching scientific literature has revealed various experimental studies illuminating different pharmacological properties of extracts and chemical constituents of the studied remedies that may contribute to their wound healing activity. The studied remedies have shown their efficiency in wound healing via four essential pharmacological activities namely, anti-inflammatory, antioxidant, and antimicrobial activities as well as wound healing activity (via modulating one or more of the wound healing phases). Seven remedies (*A. vera* leaves, *C. recutita* flowers, cuttlefish bone, honey, *L. usitatissimum* seeds, *M. communis* leaves, and *P. granatum* pericarp) were found to exert their wound healing activity by all four pharmacological activities, whereas the remaining five remedies were found to exhibit their wound healing activity either via three (*T. laevigatus* leaves), two (*M. bengalensis* leaves, potassium alum, and *R. nervosus* leaves) or one (tragacanth gum) pharmacological activities (Table 2).

The acute inflammatory response during the early stages of injury generates factors that are essential for tissue growth and repair. However, the prolonged, chronic inflammation can be detrimental, preventing wound remodelling and matrix synthesis, leading to delay in wound closure and an increase in wound pain. Thus, it is possible that an anti-inflammatory effect could facilitate wound healing and improve patient comfort, although traditional texts and animal studies indicate that extracts having anti-inflammatory effect also possess wound healing activity [8]. Eight of the studied herbal and non-herbal remedies extracts and/or their active constituents were found to possess anti-inflammatory activity (Table 2). For many of these remedies, several mechanisms of action responsible for their anti-inflammatory activity have been reported. *A. vera* leaf skin water extract was found to inhibit the proinflammatory phospholipase A2 [22]. Phospholipases A2 cleave membrane phospholipids to release arachidonic acid, the precursor to a large family of pro-inflammatory eicosanoids including prostaglandins and leukotrienes that have been proven to exacerbate numerous diseases that have an inflammatory component [260]. The inhibition of cyclooxygenase (COX) pathway and the reduction of prostaglandin E2 (PGE2) production was demonstrated by *A. vera* gel [20,28,261]. The compound aloe-emodin (an anthraquinone constituent of *Aloe vera*) also suppressed the cyclooxygenase-2 (COX-2) mRNA expression and the PGE2 production by 40μM [32]. Inhibition of COX-2 and thromboxane A2 (TxA_2) synthase were ascribed to *A. vera* extract [34], and a glycoprotein (MW 14 kDa containing 59%protein, isolated from the gel) with IC_{50} values of 19.5 ± 1.4 μM and 17.9 ± 1.3 μM, respectively [36]. Aloesin and isorabaichromone (isolated from the gel) [34] were also shown to have some inhibitory activity against COX-2 and TxA_2 synthase. TxA_2 synthase level was also reduced by aloeresin A

Table 2: Anti-inflammatory, antioxidant, antimicrobial and wound healing activities of extracts and chemical constituents of the studied herbal and non-herbal remedies

Scientific name & part used	Anti-inflammatory	Antioxidant	Antimicrobial	Wound healing activity
		Extracts/Chemical constituents		
Aloe vera leaves	• Extracts of the leaves [20,21] • Water extract of the *Aloe vera* leaf skin [22] • Gel [23-28] • Colorized (with anthraquinones) Aloe vera gel [29] • Decolorized fresh and irradiated *Aloe vera* preparations [30] • Aloin & aloe-emodin [31,32] • 8-[C-β-D-[2-*O*-*(E)*-cinnamoyl] glucopyranosyl]-2[(R)-2-hydroxypropyl]-7-methoxy-5- methylchromone [33] • Aloeresin A, aloeresin B [34] • Purified protein (molecular weight (MW) 14 kDa) [35] • Glycoprotein (MW 14 kDa containing 59% protein) [36] • Mannose-6- phosphate [26,37] • Veracylglucan B and C [38] • Sterols [39] • Gibberellins [29] • Bradykinase [20] • Carboxypeptidase [40] • Magnesium lactate [40] • Salicylic acid [41]	• Gel [42-45] • Aqueous extract of leaves [46] • Extracts of leaf skin [22,47] • Aloe-emodin [31,48,49] • 8-*C*-β-*D*-[2-*O*-(*E*)-coumaroyl] glucopyranosyl-2-[2-hydroxy] propyl-7-methoxy-5-methylchromone [50] • Isorabaichromone, aloeresin A, aloeresin B, and aloesin [34] • Dihydrocoumarin and dihydrocoumarin ethyl ester [51] • Glycoprotein (MW of 14 kDa containing 59%protein) [36] • Polysaccharides (APS-1, APS, GAPS-1 and SAPS-1 [52-54] • Vitamins (A, B, C, E, choline, folic acid), total phenols, and flavonoids [46] • Glutathione peroxidase and superoxide dismutase [46]	• Gel [20,41,55-58] • Extracts of the gel [56,59] • Ethanol extract of the leaf after removing the gel [55] • Leaf extracts [60,61] • Aloe emodin [31,56,62,63] • Aloin and emodin [64] • Acemannan and glucomannan [20] • Lectins fractions of Aloe vera gel [20] • Purified protein of 14 kDa [35] • Pyrocatechol [59] • *p*-Coumaric acid [59] • Cinnamic acid [59] • Ascorbic acid [59] • Saponins [20,41,56] • Hormones [41]	• Gel [20,28,31,65-76] • Aqueous extract of the leaves (without the rind) [77] • Methanol extract of the leaves [21] • Aloe emodin [78] • Glycoprotein fraction (5.5 kDa from the gel) [79] • Mannose-6- phosphate [26] • Veracylglucan C [38] • Aloeride [80] • Acemannan [20,68,69,81] • Mannose rich polysaccharides with molecular weight between 50 and 250 kDa [82] • Gibberellins [20,26] • Ascorbic acid [41]
Astragalus gummifer/ Labill., and other *Astragalus* species gum (Tragacanth gum)	NA*	NA	NA	• Tragacanth gel 5% [83] • 6% Tragacanth mucilage [84]
Chamomilla recutita flowers	• Extracts [68,85-91] • Essential oil [87,88] • α-Bisabolol [68,85,88,91-94] • (-)-α-Bisabololoxides A and B [68,93] • Matricin [68,88,93,95] • Chamazulene [68,85,88,92,93] • Chamaviolin and chamazulene [91] • Cis-en-yn-spiroether [88] • Apigenin, luteolin, quercetin, myricetin, apigenin-7-glucoside, rutin [68,85]	• Extract [89,96-102] • Essential oil [103] • α-Bisabolol [104-106] • Chamazulene [89,106,107] • Apigenin-7-0-(6"-acetyl)-glucoside, luteolin, apigenin, eupatolitin, and chrysosplenol D [101] • Polyphenolic-polysaccharide conjugates [108]	• Extracts [68,88,93,100,102] • Essential oil [68,88-91,100,109-111] • α-Bisabolol [85,88,91,93,112-114] • Chamazulene [88,93] • Nerolidol [91,112] • Farnesol [112] • Chamomile esters and lactones [93] • The en-yn-dicycloethers [88] • Flavonoids [93] • Umbelliferone [93]	• Extracts [68,88,90,115-121] • α-Bisabolol, chamazulene and farnesene [92]
Cuttlefish bone	• Extract (chitin as the main component) [122,123]	• Extract (chitin as the main component) [122] • Polysaccharides with a total sugar content of 86.2% extracted from the cuttlebone of *S. aculeate* [124]	• Polysaccharides [125,126]	• Extract (chitin as the main component) [122,123,127,128]
Honey	• Honey [129-131]	• Honey [130-132] • Phenolics, flavonoids, ascorbic acids, and some enzymes (glucose oxidase and catalase) present in honey [131]	• Honey [130,131,133-137]	• Honey [129-131,138]

(*Contd...*)

Table 2: ***(Continued)***

Scientific name & part used	Anti-inflammatory	Antioxidant	Antimicrobial	Wound healing activity
Linum usitatissimum **seeds oil**	• Fixed oil [139] • α-linolenic acid [139,140] • Tocopherol (vitamin E) [141]	• Flaxseed oil [142] • Flaxseed hull oil [143]	• Pteroleum ether seeds extract containing palmitic acid, linoliec acid and oleic acid [144] • Fixed oil [145]	• Fixed oil [117,141,146-148] • α-Linolenic acid-rich linseed oil [149] • Oleic acid [150] • linoleic acid [146,150] • α-Linolenic acid [146,149,150]
Meriandra bengalensis **leaves**	NA	• Essential oil of Yemeni *M. bengalensis* (very weak antioxidant activity) [151]	• Extracts of Yemeni *M. bengalensis* [152,153] • Extracts of Eritrean *M. bengalensis* [154] • Essential oil of Yemeni *M. bengalensis* [151]	NA
Myrtus communis **leaves**	• Essential oil [155] • 80% ethanol extract [156] • Myrtucommulone [157-159] • Semi-myrtucommulone [157]	• Extracts [156,160-164] • Essential oil [165] • Myrtucommulone and Semimyrtucommulone [166,167] • Myricetin 3-*O*-β-D-xyloside, myricetin 3-*O*-β-D-galactoside, myricetin 3-*O*-β-D-galactoside 6˝-0-gallate and myricetin 3-*O*-α-L-rhamnoside [168] • Myricetin 3-*o* galactoside and myricetin 3-*o*-rhamnoside from *M. communis var italica* [169] • Four hydrolyzable tannins [oenothein B, eugeniflorin D2, and tellimagrandins I and II [168] • Gallic acid and quinic acid 3,5-di-0-gallate [168]	• Extracts [156,170-176] • Essential oil [165,171,177-181] • Myrtucommulone A [182-184] • Semi-myrtucommulone [183,184] • Gallo-myrtucommulone A & B [185]	• Extract [186] • A pasta containing 5% leaves aqueous extract [187]
Potassium aluminum sulfate dodecahydrate	NA	NA	• Aqueous solution [188-191]	• Powder [192]
Punica granatum **pericarp**	• Extracts [193-196] • Standardized pomegranate rind extract containing 13% w/w ellagic acid [197-199] • Punicalagin, punicalin, strictinin A, and granatin B [200]	• Extracts [196, 201-217] • Gallocatechin, gallocatechin-(4-8)-catechin, gallocatechin-(4-8)-gallocatechin and catechin-(4-8)-gallocatechin [218] • Gallic acid [219] • Ellagic acid [219,220] • Punicalagin [219-222] • Punicalin [219,220]	• Extracts [197,210,219,223-236] • Tannins [237] • Ellagitannins and those with galloyl or hexahydroxydiphenoyl groups including casuarinin and corilagin [214,225] • Monomer and dimer ellagitannins, gallotannins and polyphenols [214] • Punicalagin [229,238] • Punicalin, granatins A and B, gallagyldilacton, casuarinin, pedunculagin, tellimagrandin I and corilagin [229]	• Extracts [210,230,233,234, 239-242]
Rumex nervosus **leaves**	NA	• Extracts [243-245]	• Extracts [243,245-249] • The oil (containing methyl esters of palmitoleic acid (28.35%), palmitic acid, (25. 37%) and stearic acid (20.25%) as the major components) [245]	NA
Thymus laevigatus **leaves**	• Thymol [250] • Carvacrol [251]	• Methanol and dichloromethane extracts [252] • Essential oil [253,254] • Thymol [254]	• Extracts [246,252] • Essential oil [255,256] • Thymol [257-259] • Carvacrol [258,259]	NA

NA* = data not available

and B (isolated from the gel) with IC_{50} value of 58 μM and 13.6 μM, respectively [36]. A dual inhibition of pure lipoxygenase (LOX) and COX-2 was shown by a purified protein (MW 14 kDa) isolated from *A. vera* gel [35]. Other mechanisms of anti-inflammatory action of *A. vera* and its constituents include the significant inhibition of polymorphonuclear leukocyte infiltration into a site of a 2% gelatine-induced inflammation in streptozotocin-induced diabetic mice by colorized (with anthraquinones) *Aloe vera* gel (68.0% inhibition at 100 mg/kg, $P<0.001$) and gibberellin (60.0% inhibition at 100 mg/kg, $P<0.001$) [29], the downregulation of the expression of inflammatory mediators such as interleukin (IL)-6, IL-8 and intercellular adhesion molecule (ICAM)-1, which was demonstrated to be stronger and significant by veracylglucan C than by veracylglucan B [38], and the inhibition of the inducible nitric oxide synthase (iNOS) mRNA expression and nitric oxide (NO) production by aloe-emodin at 5- 40 μM and the suppression of the production of NO by aloin at 5-40μM [32], as well as the antibradykinin activity demonstrated by a purified gel fraction (67% inhibition of bradykinin-induced contraction of the isolated rat ileum) [27], and by the enzyme carboxypeptidase (inactivation of bradykinin) of *A. vera* [40]. In addition, histamin release and formation was inhibted by aloin (70% inhibtion of histamin release comparing with indomethacin (35%) [262], and magnesium lactate [40], respectively. *C. recutita* flowers aqueous extract was reported to inhibit PGE2 prodiction due to the suppression of the COX2 gene expression and direct inhibition of COX2 enzyme activity [263], while supercritical carbon dioxide extract was found to inhibit 5-LOX, COX and the oxidation of arachidonic acid with IC_{50} of 6-25 μg/ml [88]. Several *C. recutita* flowers constituents were found to inhibit COX and LOX enzymes; chamaviolin and chamazulene carboxylic acid inhibited COX-2 [91], apigenin inhibited 5- and 12-LOX (IC_{50} = 8 μM and 90 μM, respectively), chamazulene and (-)-α-bisabolol inhibited 5- LOX (IC_{50} = 13 μM and 40 μM, respectively),while apigenin, cis-en-yn-spiroether and (-)-α-bisabolol inhibited COX (IC_{50} = 70-80 μM) and both bisabolol and bisabolol oxide inhibited 5- LOX, although bisabolol was the more active of the two compounds [88]. Moreover, α-(-)-bisabolol [94] and matricine [95] were found to inhibit the production of proinflammatory cytokines (tumor necrosis factor (TNF)-α and IL-6) and the nuclear factor kappa B (NF-κB) signalling, respectively. Cuttlefish bone was demonstrated to reduce of the levels of white blood cells, TNF-α, and IL-6 [122]. Honey was reported to reduce the numbers of inflammatory cells present in wounds [129,130]. *L. usitatissimum* seeds fixed oil was found to inhibit the prostaglandin 2-, leukotriene-, histamine-, bradykinin-, and arachidonic acid-induced inflammation [139]. *L. usitatissimum* seeds constituents, α-linolenic acid and tocopherol, have been shown to inhibit COX and LOX pathways [140] and to attenuate proinflammatory cytokines and chemokines production [141], respectively. *M. communis* leaves essential oil, topically applied, was found to inhibit the migration of neutrophils to the inflamed area and the TNF-α and IL-6 formation [155]. In addition, the 80% ethanol leaves extract was reported to reduce the COX-2 and iNOS expression level in lipopolysaccharide (LPS)-stimulated J774A.1 macrophage by 10.50 ± 3.59 fold ($P<0.05$) and 26.73 ± 3.05 fold ($P < 0.01$), respectively versus control group [156]. *M. communis* leaves constituents (myrtucommulone (MC), and semimyrtucommulone (SMC) have been shown to inhibit COX-1 and 5-LOX directly at IC_{50} values in the range of 1.8 to 29 μM, and prevent the mobilization of Ca^{2+} in polymorphonuclear leukocytes, mediated by G protein signalling pathways at IC_{50} values of 0.55 μM and 4.5 μM, respectively, as well as suppress the formation of reactive oxygen species and the release of elastase at comparable concentrations [157]. In addition, MC has been shown to inhibit the microsomal PGE2 synthase-1 and reduced the formation of PGE2 (in three different assays (cell-free, cellular, and whole blood assays at approximately IC_{50} values of 1 to 3 $\mu mol \cdot L^{-1}$) without significant inhibition of the COX enzymes. The SMC also inhibited mPGES-1 activity, although less potently (IC_{50} = 10 μmol·L-1) [159]. Moreover, MC was found to exert anti-inflammatory activity, in two *in vivo* models of acute inflammation in mice by decreasing carrageenan-induced paw edema (68% inhibition at 4.5 mg/kg i.p. pretreatment comparing to 57% inhibition by the reference indomethacin at 5mg/kg) and reducing the inflammation in carrageenan-induced pleurisy model (MC ,4.5 mg/kg i.p. 30 min before and after carrageenan, reduced the exudate volume and leukocyte numbers, lung injury and neutrophil infiltration, lung intercellular adhesion molecule-1, P-selectin immunohistochemical localization, TNF-α, IL-1β levels in the pleural exudate and their immunohistochemical localization in the lung, leukotriene B4 level in the pleural exudates, lung peroxidation and nitrotyrosine and poly(ADP-ribose) immunostaining) [158]. Pomegranate rind aqueous extract, applied topically to *ex vivo* skin, has been demonstrated to downregulate the expression of COX-2 more than the total pomegranate tannins [219,235], while the aqueous ethanol and methanol extracts were found to inhibit the NO production induced by LPS by 67% in comparison to dexamethasone (95%) [195], and the release of endogenous inflammatory mediators [194], respectively. It has been shown that a standardized pomegranate rind extract containing 13% w/w ellagic acid was a potent inhibitor of the NO production [197] and its topical application had an excellent anti-inflammaotry effect due to the inhibition of leukocyte infiltration and blockage of the proinflammatory cytokines [198]. The pomegranate peel constituents, punicalagin, punicalin, strictinin A, and granatin B were found to inhibit NO production and iNOS expression in RAW 264.7 cells. Among them, granatin B showed the strongest iNOS and COX-2 inhibitory effects [200]. In addition, ellagic acid, punicallin and punicalagin were reported to decrease the mRNA expressions of the pro-inflammatory factors, TNF-α, interferon gamma (IFN-γ) and IL-6, in oxidatively stressed mice [220]. The anti-inflammatory mechanism of action of *T. laevigatus* leaves has not been yet illustrated. However, the compounds, thymol and carvacrol, were reported to exert anti-inflammatory activities; thymol inactivated calcium channels machinery and thus triggered a corresponding reduction of elastase release [250] and carvacrol inhibited the production of PGE2 catalysed by COX-2 with an IC_{50} value of 0.8μM, similar to standard inhibitors indomethacin and NS-398 with IC_{50} values of 0.7 μM and 0.8 μM, respectively. The COX-1 was also inhibited by carvacrol approximately at the same rate (IC_{50} = 0.7 μM), which suggests non-selective

inhibition of both enzyme isoforms [251]. These compounds (carvacrol (84%) and thymol (52.46%) were reported to be the main constituents of the volatile oils obtained from the leaves of the Yemeni *T. laevigatus* growing in Haggah [252] and Sana'a [253], respectively.

The production of free radicals at or around the wound bed may contribute to delay in wound healing through the destruction of lipids, proteins, collagen, proteoglycan, and hyaluronic acid. Agents that demonstrate a significant antioxidant activity may, therefore, preserve viable tissue and facilitate wound healing [8]. Principal mechanisms applied by antioxidant compounds include the scavenging of free radicals, the reduction of metals such as iron and copper, creating complexes with metal pro-oxidants (chelating), quenching single oxygen, and stimulating antioxidative defense enzymatic activities (decreasing the cellular level of free radicals either by inhibiting the activities or expressions of free radical generating enzymes such as NAD(P)H oxidase and xanthine oxidase or by enhancing the activities and expressions of endogenous antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase and increasing cellular antioxidants). The methods used for evaluating the antioxidant activity frequently depend on the reaction mechanisms of the antioxidants. These antioxidants are capable of inactivating radicals with two major mechanisms of hydrogen atom transfer (HAT) and single electron transfer (SET). HAT-based methods measure the ability of antioxidants to disable free radicals by hydrogen donating. SET-based methods detect the ability of antioxidants to transfer single electron to reduce any compound, including metals, carbonyls, and radicals [264,265]. Ten of the herbal and non-herbal remedies extracts and/or their chemical constituents (Table 2) were found to possess antioxidant activity and their ability to scavenge free radicals, reduce metals, chelate metal catalysts, and activate antioxidant enzymes and prevent lipid peroxidation has been proved by several *in vivo* and *in vitro* assays. *A. vera* gel [45], aqueous extract of A. *vera* leaves (without the gel) [46], chloroform-ethanol (1/1), ethyl acetate, hexane [22] and methanol [47] extracts of A. *vera* leaf skin as well as *A. vera* constituents such as dihydrocoumarin and dihydrocoumarin ethyl ester [51], aloesin derivatives (isorabaichromone, aloesin, aloeresin A and aloresin B) [34], several polysaccharides, viz APS-1 [52], APS [54], GAPS-1 and SAPS-1[53], aloe-emodin [49] and glycoprotein (m.w. 14 kDa) [36] were reported to scavenge one or more of 1,1 diphenyl-2-picrylhydrazyl (DPPH$^{\bullet}$), 2,2´-azino-bis(3-ethylbenzo-thiazoline-6-sulfonic acid (ABTS$^{+\bullet}$), NO, superoxide anion ($O_2^{\bullet-}$), hydroxyl $^{\bullet}$OH, and alkyl free radicals as well as hydrogen peroxide. In addition, *A. vera* gel [43], and its ethanol extract [42], the aqueous extract of the leaves (without the gel) [46], as well as the constituents, namely, 8-C-β-*D*-[2-*O*-(*E*)-coumaroyl] gluco-pyranosyl-2-[2-hydroxy] propyl-7-methoxy-5-methyl-chromone [50], isorabaichromone, and aloeresin B [34], the polysaccharides, APS-1[52], GAPS-1 and SAPS-1[53] as well as aloe-emodin [31,48,49] were found to suppress lipid peroxidation. Other antioxidant activities reported for *A. vera* extract and constituents were the reduction of the levels of reactive oxygen species in oxidative stressed Vero cells by the polysaccharide APS [54], the ferric reducing antioxidant activity by the methanol extract of leaf skin [47] and the polysaccharides GAPS-1 and SAPS-1 [53], as well as the ferrous chelating effects by GAPS-1 and SAPS-1 [53]. Moreover, *A. vera* gel [43], its ethanol extract [42,44] and the polysaccharide APS-1 [52] were reported to recover or increase the reduced activities of the antioxidant enzymes such as SOD, CAT, glutathione peroxidase, glutathione-S-transferase and glucose-6-phosphate dehydrogenase as well as glutathione, and uric acid. *C. recutita* flower extracts, namely, methanol [100], aqueous [102], 70% ethanol [97], ethyl alcohol-water (1:1) [99], 70% aqueous methanol [101], and water, ethanol and methanol [98] extracts as well as the essential oil [103,266] and the constituents of *C. recutita* flowers viz, the flavonoids (apigenin-7-O-(6"-acetyl)-glucoside, luteolin, apigenin, eupatolitin, and chrysosplenol D) [101], α-bisabolol and chamazulene [106], and α-bisabolol oxide A and (E)-β-farnesene [266] were found to scavenge DPPH$^{\bullet}$ radicals. Polyphenolic-polysaccharide conjugates isolated from flowering parts of *C. recutita* displayed DPPH$^{\bullet}$ and ABTS$^{+\bullet}$ radicals scavenging activity [108]. Inhibition of lipid peroxidation was demonstrated by dichloromethane extract of the distillate [96], ethyl alcohol-water (1:1) [99], water, ethanol, and methanol [98] extracts, and the essential oil [103] of *C. recutita* and its constituent chamazulene [89]. Pre-incubation of blood plasma with chamomile polyphenolic-polysaccharide conjugates was also found to diminish significantly the extent of $ONOO^-$-induced oxidative stress of the biomarkers of blood plasma proteins such as protein carbonyl and thiol groups, nitrated proteins, and the formation of lipid hydroperoxides [108]. It has been demonstrated that chamomile water extract [102] showed ferric reducing activity and the polyphenolic-polysaccharide conjugates [108] increased the ferric reducing ability of blood plasma. Moreover, α-bisabolol was reported to inhibit both the reactive oxygen species production during human polymorphonuclear neutrophil bursts [104] and the upregulation of H_2O_2-generated free radicals in human skin fibroblasts *in vitro* [105]. Polysaccharides with a total sugar content of 86.2% extracted from the cuttlebone of *Sepia aculeate* were found to possess scavenging activity against DPPH$^{\bullet}$, superoxide and hydroxyl radicals as well as ferrous ion-chelating effect [124]. Cuttlefish bone (CB) ointment (CB extract: white petroleum 4:6) was shown to inhibit lipid peroxidation [122]. Honey treatment of patients with partial-thickness burns was reported to decline the levels of serum lipid peroxide [132]. *L. usitatissimum* seed hull oil was shown to exhibit DPPH$^{\bullet}$ scavenging activity [143]. Yemeni *M. bengalensis* leaves essential oil was found to possess very weak DPPH$^{\bullet}$ scavenging activity [151]. Different extracts (methanol, ethanol, ethyl acetate, and water) of *M. communis* leaves were found active as DPPH$^{\bullet}$ scavengers [156,161-164]. Among the constituens (four hydrolyzable tannins (oenothein B , eugeniflorin D2 , and tellimagrandins I and II), two related polyphenolic compounds (gallic acid and quinic acid 3,5-di-O-gallate), and four myricetin glycosides [myricetin 3-*O*-β-D-xyloside, myricetin 3-*O*-β-D-galactoside, myricetin 3-*O*-β-D-galactoside 6″-O-gallate, and myricetin 3-*O*-α-L-rhamnoside) isolated from the *M. communis* leaves, the four hydrolyzable tannins were found to exhibit potent DPPH$^{\bullet}$ radical scavenging activity[168]. Furthermore, myricetin-3-*O*-galactoside and myricetin-3-*O*-rhamnoside

isolated from *M. communis* var *italica* were reported to exhibit DPPH$^{\bullet}$ radical scavenging activities, and potent inhibitory effects on xanthine oxidase activity and its ability to generate the superoxide anion $O_2^{\bullet-}$ radicals [169]. Anti-lipid peroxidation activity evaluated by using several test systems was ascribed to *M. communis* leaves 70% ethanol extract, and its fractions (ethyl acetate and aqueous extracts) [160], methanol, ethanol and water extracts [163], and methanol extract [164], essential oil [165], and constituents such as semi-myrtucommulone and myrtucommulone [166,167], myricetin-3-O-galactoside and myricetin-3-O-rhamnoside [169]. Moreover, the ethanol, methnol and water extracts of *M. communis* leaves were reported to exhibit ferric reducing antioxidant activity [156,162-164]. *P. granatum* fruit peel extracts, namely, methanol [196,201,217], 75% aqueous methanol [210], ethanol [206,215], water [217] extracts, methanol, ethanol and acetone fractions [208], a mixture of methanol, ethanol, acetone and water extract [204] and ellagic acid rich extract [209] were found to exhibit scavenging activity against one or more of DPPH$^{\bullet}$, ABTS$^{\bullet+}$, hydroxyl, peroxyl and nitric oxide radicals. The active constituent of *P. granatum* fruit peel, punicalagin, was found able to scavenge ABTS$^{\bullet-}$ radicals and repair ABTS$^{\bullet-}$, guanosine, and tryptophan radicals, generated by pulse radiolysis, via electron transfer [221]. In addition, commercial standard punicalagin was reported to possess DPPH$^{\bullet}$ radicals and H_2O_2 scavenging activity [222]. Moreover, punicalagin, punicallin and ellagic acid were shown to scavenge DPPH$^{\bullet}$ and $O_2^{\bullet-}$ [220] and the prodelphinidin dimers (gallocatechin-(4-8)-catechin, catechin-(4-8)-gallocatechin and gallocatechin-(4-8)-gallocatechin) were found more potent ABTS$^{\bullet+}$ radical scavengers than the gallocatechin monomer [218]. Lipid peroxidation was reported to be inhibited by the extracts and some constituents of *P. granatum* fruit peel as follows: methanol extract [201,202,207], 75% aqueous methanol extract [210], 50% aqueous methanol extract [211], ethanol extract [207,216], acetone and chloroform extracts [207] and a mixture of methanol, ethanol, acetone and water extract [204]; punicalagin [220,221], punicallin and ellagic acid [220] as well as gallocatechin-(4-8)-catechin [218]. Moreover, methanol extract was found to strongly protect LDL from oxidation [201]. Antioxidant activity by increasing endogenous antioxidant enzymes such as SOD, CAT, and gluthathione peroxidase in normal experimental animals was shown by the 50% aqueous methanol extract of *P. granatum* fruit peel [211], while preserving or increasing of such enzymes in oxidatively stressed experimental animals were demonstrated by the methanol extract [202] and by punicalagin, punicallin and ellagic acid, respectively [220]. The ability to reduce one or more of the metal ions such as iron in the ferric reducing antioxidant power assay, copper in the cupric reducing antioxidant capacity assay or molybdenum in phosphomolybdenum method has been demonstrated by a number of *P. granatum* fruit peel extracts and constituents such as ethanol extract [215], ethyl acetate extract [212], methanol, ethanol, acetone and ethyl acetate fractions [208], ethyl acetate, acetone, and methanol extracts [203], a mixture of methanol, ethanol, acetone and water extract [204,205], as well as by punicalagin [220,222], ellagic acid and punicallin [220]. Furthermore, the compound punicalagin was found to possess chelating ability toward iron [222]. Yemeni *R. nervosus* leaves extracts such as the methanol extract [243], crude methanol extract and its sub fractions (ethyl acetate, methanol, *n*-hexane and chloroform) as well as the oil (containing the methyl esters of palmitoleic acid (28.35%), palmitic acid, (25. 37%) and stearic acid (20.25%) as the major constituents) [245] have been demonstrated to exhibit DPPH$^{\bullet}$ radical scavenging activity. Ethiopian *R. nervosus* leaves ethyl acetate extract was reported to exhibit DPPH$^{\bullet}$, ABTS$^{\bullet+}$ and $O_2^{\bullet-}$ radical scavenging activities, Fe^{2+} chelating activity, and ferric reducing antioxidant activity [244]. DPPH$^{\bullet}$ scavenging activity was also shown by the methanol and dichloromthane extracts of Yemeni *T. laevigatus* leaves collected from Haggah [252], and the essential oil of Yemeni *T. laevigatus* leaves collected from Sana'a containing high amount of thymol (52.46%) [253]. The essential oil of the aerial part of Pakistani *T. serpyllum* (its synonym = *T. laevigatus*), containing carvacrol as the major component, was found to exhibit higher DPPH$^{\bullet}$ scavenging activity and lipid peroxidation inhibitory effect than carvacrol [254]. Thymol was also found to scavenge DPPH$^{\bullet}$ radicals and inhibit lipid peroxidation [254]. Table S1 (supplementary materials) presents more details on the mechanisms of the antioxidant activity of the studied remedies.

Wound healing can be delayed when microorganisms are present in large numbers. Therefore, reducing the bacterial load of a wound may be necessary to facilitate wound healing as well as to reduce local inflammation and tissue destruction [8]. Different extracts and isolated compounds from the studied herbal and non-herbal materials, except of tragacanth gum (Table 2), were found to possess antimicrobial activity against a wide array of microorganisms, including multi - resistant strains. The mechanisms of action for the antimicrobial activity were reported for some of the extracts and chemical constituents of these remedies. The antimicrobial activity of *A. vera* leaves constituents was ascribed to a number of mechanisms such as the inhibition of the microorganisms enzyme, penicillinase, by rhein, emodin and aloe-emodin [267], the inhibitory effect of aloe emodin on the initial adhesion and proliferation stages of *Staphylococcus aureus* biofilm development [63] and the partial disruption of virus envelopes of herpes simplex virus type 1 and type 2, varicella-zoster virus, pseudorabies virus, and influenza virus [62]. In addition, aloe emodin antibacterial and antiviral effects was attributed to the inhibition of nucleic acid biosynthesis after which protein synthesis is also inhibited [31]. Lectins and fractions of *A. vera* gel were reported to produce a direct inhibition of the cytomegalo virus proliferation in cell culture, perhaps by interfering with protein synthesis [20]. On the other hand, acemannan, an active constituent of *A. vera* gel, was found to possess indirect antimicrobial activity through its ability to stimulate phagocytic leukocytes [56]. *C. recutita* flowers essential oil was demonstrated to possess a virucidal activity against herps viruses by interfering with virion envelope structures or by interrupting their adsorption [110,111]. Enhancement of the susceptibility of *S. aureus* to a number of antibiotics (ciprofloxacin, clindamycin, erythromycin, gentamicin, tetracycline, and vancomycin) by *C. recutita* flowers constituents (nerolidol, farnesol and bisabolol) was attributed to the disrupting of the normal barrier function of the bacterial cell membrane, allowing the permeation of the

antibiotics. This effect is more pronounced for Gram-positive bacteria, probably due to the lack of additional permeability barriers, particularly the outer membrane of Gram-negative bacteria [112]. The antibacterial properties of honey was connected to a complex interplay of various components of honey, namely, its high osmolarity, acidity, presence of bacteriostatic and bactericidal factors (hydrogen peroxide, nitric oxide, antioxidants, lysozyme, polyphenols, phenolic acids, flavonoids, methylglyoxal, bee defensin-1, and bee peptides) [130,131,136,137]. Moreover, controlling wounds malodor by honey was attributed to its antimicrobial action against odor producing bacteria and supplying copious quantity of glucose as substrate, which bacteria metabolise in preference to amino acids, from decomposed serum and tissue proteins, which are converted to malodorous substances ammonia, amines, and sulfur compounds [130,131]. Linoleic acid, a constituent of *L. usitatissimum* seeds was found to inhibit the growth of *S. aureus* by increasing the permeability of bacterial membrane due to its surfactant action [268]. *M. communis* extract and essential oil were reported to affect mainly the permeability of bacterial cell wall and cell membrane leading to the release of intracellular contents outside of cell and this can be accompanied with the disruption in the membrane functions such as electron transfer, enzyme activity or nutrient absorption [174]. The antifungal (against a number of *Candida* species (*C. krusei*, *C. guilliermondii*, *C. parapsilosis*, *C. lusitaniae* and *C. rugosa*)) and the antiviral activities of *P. granatum* L. fruit peel extract were shown to be due to morphological alterations , cell aggregation and growth inhibition of fungi [229] and impeding viral attachment and penetration via disruption of the glycosylation of viral glycoproteins [219]. The antimicrobial mechanism of action of the leaves of *T. laevigatus* Vahl. has not been yet illustrated. However, the antimicrobial mechanisms of action of the compounds ,carvacrol and thymol, which are also the major constituents of essential oils of Yemeni *T. laevigatus* Vahl leaves, growing in different areas, [252,253] were demonstrated by their ability to permeabilize, depolarize, and disrupt the cytoplasmic membrane, and inhibitory effect on biofilm formation (inhibiting the growth of preformed biofilm and interfering with biofilm formation during planktonic growth) as well as by their antifungal activity (changing cell membrane fluidiy and permeability, and changing the morphogenesis of the envelope of *C. albicans*) [259].

Wound healing is a dynamic and complex process involving a series of co-ordinated events, including bleeding, coagulation, initiation of an acute inflammatory response to the initial injury, regeneration, migration and proliferation of connective tissue and parenchyma cells, as well as synthesis of extracellular matrix proteins, remodelling of new parenchyma and connective tissue and collagen deposition and finally, increasing the wound strength that takes place in an ordered manner and culminates in the repair of severed tissues [12]. Nine of the herbal and non-herbal remedies were found to promote wound healing (Table 2). These remedies were reported to speed wound healing by several mechanisms of action including stimulating a variety of specialized cells, such as macrophages, fibroblasts, and epithelial cells and the action of cytokines, chemokines and growth factors that regulate the cellular functions during different wound healing phases as well as activating the cellular immune system. Regarding the wound healing activity of *A.vera* gel, there are many contradictions. Some studies, for example, showed that *Aloe vera* promoted the rates of healing, while, in contrast, other studies showed that wounds to which A. *vera* gel was applied were significantly slower to heal than those treated with conventional medical preparations [31,38,69,82]. Searching literature data has indicated that A. *vera* gel exerts its wound healing activity by several mechanisms of action such as keeping the wound moist, insulating and protecting, reducing inflammation, increasing epithelial cell migration, promoting collagen formation and maturation, enhancing fibroblast proliferation, direct stimulating the activity of macrophages and fibroblasts, and thus increasing collagen and proteoglycan synthesis, increasing the synthesis of glycosaminoglycans of the matrix, acting as an inhibitor of thromboxane A2 (a mediator of progressive tissue damage), promoting cell growth and attachment, increasing epithelialization and angiogenesis, accelerating wound contraction and wound closure as well as increasing oxygen access as a result of increased blood supply and stimulating the complement linked to polysaccharides [26,41,67-71,73,74]. The aqueous extract of A. *vera* leaves (without the rind) was shown to accelerate epithelialization, wound contraction, tissue alignment and tissue strength at the later stage of wound healing [77]. The following A. *vera* gel active constituents were found to promote wound healing by a number of mechanisms of action: aloe emodin increased the rate of wound healing, reduced the wound area, stimulated re-epithelialization and promoted angiogenesis as a result of the stimulation of vascular endothelial growth factor (VEGF) due to an increase in the expression of IL-1β in macrophages [78], acemannan acted as macrophage activator, and stimulated fibroblast proliferation and granulation tissue formation [20,68,69], glucomannan activated macrophages and both glucomannan and acemannan stimulated immune system and possessed antibacterial and antiviral activities [20], aloeride activated transcription factor NF-kappa B and macrophages [80], mannose 6-phosphate (via binding to the insulin like growth factor receptors) stimulated the fibroblast to increase collagen and proteoglycans production and hence to increase wound tensile strength [26], mannose rich polysaccharides with molecular weight between 50 and 250 kDa regulated matrix metallopeptidase (MMP-3) and the metallopeptidase inhibitor-2 gene expression during the dermal wound repair that might also influence the granulation tissue formation and wound closure by increased production of extracellular matrix constituents including glycosaminoglycans and collagen [82], glycoprotein fraction with a molecular weight of about 5.5 kDa enhanced keratinocyte multiplication and migration, expression of proliferation of related factors, and epidermis formation [79]. In addition to the above mentioned anti-inflammatory activity of both veracylglucan B (Vglc B) and veracylglucan C (Vglc C), Vglc C was found to exhibit a significant cell proliferative effect at 100μg/mL (slightly superior to that of human platelets-derived growth factor (PDGF) at the same concentrations), while Vglc B showed a significant cell anti-proliferative effect at 1mg/mL. A remarkable antagonism of the proliferative effect of Vglc C through Vglc B was also demonstrated in this study [38]. To understand some of the reasons behind many

contradictions about the therapeutic properties of A. *vera* gel, and by considering that wound healing involves cell proliferation and that a recombinant PDGF (Becaplermin®) is available as a remedy for poor wound-healing by diabetic ulcers, the authors concluded that Vglc C is the compound in *Aloe vera* gel, which is responsible for the wound healing properties and the anti-proliferative activity of Vglc B is, on the other hand, responsible for the retardation and cancellation of significant healing effects arising from Vglc C, and depending on the variations in the concentration of these bioactive maloyl glucans and contamination with anthranoids (e.g., aloin) as a result of the cultivation in different climatic zones, harvesting and processing (stability problems) of *Aloe barbadensis* Miller to *Aloe vera* gel, the gel containing higher amount of Vglc B or anthranoids will lead to retardation of wound healing, while higher quantities of Vglc C would definitely foster wound healing [38]. Further constituents of A. *vera* such as ascorbic acid and gibberellin were found to enhance the synthesis of collagen and counterbalance collagen breakdown [41], and to stimulate fibroblasts activity and proliferation [20], respectively. The wound healing activity of *C. recutita* flowers extracts was attributed to their ability to produce wound drying and speed re-epithelialization after dermabrasion [68], accelerate burn wounds cleansing and improve granulation [88], exhibit marked dryness of wound margins with tissue regeneration and reduce wound area [116] and increase wound contraction, together with the increased wound-breaking strength, and hydroxyproline content [90]. Chamomile active constituents such as (-)-α-bisabolol and chamazulene were reported to shorten the healing time of cutaneous burns of guinea pigs in which (-)-α-bisabolol caused a stronger blood ciruculation. In addition, both the (-)-α-bisabolol and farnesene promoted epithelization and granulation [92]. Hydrocolloidal membrane containing cuttlefish bone (CB) was found effective in healing rats wounds by significant improving in scar tissue reduction, epithelium regeneration, angiogenesis, and extracellular matrix deposition in wound area [128]. Moreover, CB ointment (CB extract: white petroleum = 4:6)) was shown to exhibit wound healing activity of thermal burn wounds in rats by reducing the levels of white blood cells, and the expression of TNF-α, and IL-6 at late time, as well as by inhibition of lipid peroxidation and promoting re-epithelialization. These effects are comparable to those of silver sulfadiazine [122]. Testing CB extract by the same authors has revealed that treating murine macrophage cell line (RAW 264.7 cells) with CB extract induced the activation of macrophages and increased the production of pro-inflammatory cytokins such as TNF-α, IL-1β, and IL-6 as well as transforming growth factor-beta (TGF-β), VEGF and NO. On the other hand, it has been found that CB extract suppressed the production of TNF-α, IL-1β, and IL-6 cytokines in macrophages activated with LPS suggesting that CB may protect the cell and tissue from injury or destruction at high concentration of cytokines. In addition, CB extract was found to enhance proliferation of murine fibroblast and induce the activation of fibroblast to increase the expression of the matrix metalloproteases MMP1 gene and the secretion of MMP1 protein in fibroblasts, which may play an important role in the regulation of acute inflammatory reaction in a pathologic status such as burn. Furthermore, CB extract induced the production of IL-8 in macrophages, which is related to the cell migration, and treatment with CB was found to enhance fibroblast migration and invasion [123,127]. Chitin was characterized as the main component of cuttlebone by using FT-IR [122], and HPLC [127] methods. Applying scanning electron microscope indicated almost no difference in morphology between CB extract and chitin [123]. It has been concluded that the proposed mechanism of CB extract to promote healing of burned lesion of rats was associated with that chitin in CB extract, which stimulated wound skins to induce acute inflammation and promoted cell proliferation and MMP expression in fibroblast [127]. In addition, it was reported that chitin activated macrophages by interacting with cell surface receptors such as mannose receptor and toll-like receptor-2 and chitin- activated macrophages enhanced the formation of tissue in the wound by migrating inflammatory cells and the production of endothelial growth factor. Furthermore, chitin is known to play an essential role in homeostasis [123,127]. The wound healing activity of honey has been attributed to several mechanisms such as its ability to create a moist environment and consequently provide a constant flow of nutrients, help with oxygenation, supply glucose to the epithelial cells, give a constantly replenished supply of proteases to facilitate the rapid debridement of wounds, and activate proteases during debridement, promote the formation of granulation tissue, and wound epithelialization, stimulate angiogenesis, tissue growth and the synthesis of collagen, increase wound contraction, improve of the strength (cross-linking) of collagen, and tensile strength of the wounds. Moreover, it has been demonstrated that honey may work also by stimulating the activity of the immune system, e.g. by promoting the proliferation of peripheral blood B- and T-lymphocytes in cell culture, activating phagocytes from blood, stimulating monocytes in cell culture to release the cytokines TNF-α, IL-1 and IL-6, and augmenting the immune response by supplying glucose that is essential for the 'respiratory burst' in macrophages, as well as providing substrates for glycolysis, the major mechanism of energy production in the macrophages [130,131]. *L. usitatissimum* seeds oil has been shown to exhibit wound healing by several mechanisms of action including cicatrizing and emollient effects, less inflammatory cells in the period of re-epithelization, shortening the inflammatory stage, completing epithelium regeneration, discreet fibrosis, enhancing neo-vascularization, increasing number of collagen fibers, fibroblasts and many myofibroblasts, improving migration of fibroblasts, higher wounds contraction and shortening the healing period [117,141,146,148,149]. A topical administration of a semisolid formulation of linseed oil (SSFLO) (1% or 5%) composed of commercial linseed oil in petroleum jelly was found to promote a significant ($P < .05$) complete re-epithelialization of skin wounds in 100% of the animals treated compared to negative control (petroleum jelly) at the end of the experiment (14 days), but the same was not observed in groups treated with 10% SSFLO and linseed oil. The authors explained this phenomenon by the greater dermal absorption of ω-3 polyunsaturated fatty acid that presents in higher concentration in the10% SSFLO and linseed oil than in 1 or 5% SSFLO and its effect on delaying wound healing. Moreover, a significant ($P < .05$) amount of inflammatory cells in scar tissue was observed in the group

treated with 10% SSFLO compared to negative control (petroleum jelly) at the end of the experiment (14 days) [147]. It has been demonstrated that *M. communis* leaves methanol extract and 10% methanol extract cream (70% methanol in paraffin oil) accelerated the healing of second-degree burn wounds in rats, comparing to sliver sulfadiazine 1%, by increasing the revascularization and fibroblast cell proliferation [186], and promoted the healing of wounds in rats by increasing wound closure, hair follicle and blood vessel numbers, skin thickness and collagen fibers [269], respectively. In addition, 80% ethanol extract (1.5 μg/mL) of *M. communis* leaves was found to increase the protein expression of angiogenic markers (hypoxia-inducible factor-1α (HIF-1α) and VEGF in human umbilical vein endothelial cells [156]. The wound healing activity of potassium alum was reported to be due to its adstringent property that causes contraction of tissues, constriction of blood vessels, extraction of water from tissue and precipitation of proteins, which leads to decreased capillary permeability, hardening of the capillary endothelium and reduction in oedema, inflammation and exudates [192,270]. Different extracts of *P. granatum* L. fruit peel such as aqueous extracts (10% and 20%) [240], 70% ethanol extract [234], a 5% (w/w) 75% methanol extract based-ointment [210] and a 10% and 15% (w/w) methanol extract based- ointment [241] were shown to enhance the healing of burn wounds and wounds by increasing wound contraction, reducing the period of epithelization and enhancing epithelialization. In addition, 70% ethanol extract was found to increase mean wound contraction (97 %) of deep second-degree skin burns in rats comparing to silver sulfadiazine (79 %) and its effect was comparable to the silver sulfadiazine in improving various phases of wound healing (reduction of inflammatory cells, increase in the formation of fibroblast, granulation tissues, collagen fibers, epithelialization and angiogenesis) [233]. Moreover, ethanol-water (3:1) extract showed wound healing percentage of 94.83% ± 0.44 comparing to the reference phenytoin with 96.00% ± 0.29 of rat's wounds after 14 days. Its effect on reducing the number of immune cells and accelerating the second stage of the healing (increasing epithelialization, neovascularization, fibroblast proliferation), and the migration of fibroblast to the wounded tissue is comparable with phenytoin [242]. Tragacanth gum gel 5%, applied topically was found to heal rats skin wounds by significant increasing of wound closure and by its high wound healing index that incorporates two factors of granulation tissue formation and epithelial regeneration [83]. Healing of skin wounds in rabbit by a 6% tragacanth mucilage (in eucerin base), topically applied, was attributed to a significant shortening of the period of wound healing and closure, which is suggested to be due to an acceleration of collagenation and proliferation phases of the wound repair [84].

Various phytochemical constituents, isolated from the studied herbal and non-herbal remedies, were found to contribute in wound healing activity via one or more of their pharmacological activities (anti-inflammatory, antioxidants, and antimicrobial activities as well as the promotion of one or several phases of wound healing process) (Table 2). These bioactive constituents belong to carbohydrates (monosaccharides (mannose-6-phosphate), disaccharide (veracylglucan B), oligosaccharide (veracylglucan C) and the polysaccharides (acemannan, glucomannan, aloeride, mannose rich polysaccharides and several other polysaccharides designated as APS- 1, APS, GAPS-1 and SAPS-1, obtained from *Aloe vera*, and the polysaccharides of cuttlefish bone and chitin as the main constituent of cuttlefish bone), phenolic compounds such as simple phenol (pyrocatechol), phenolic acids (salicylic acid, p-coumaric acid, gallic acid, ellagic acid), polyphenolic compounds (myrtucommulone, semimyrtucommulone, gallo-myrtucommulone A & B), flavonoids (apigenin, apigenin-7-O-(6"-acetyl)-glucoside, apigenin-7-glucoside, chrysosplenol D, eupatolitin, luteolin, myricetin, myricetin derivatives, quercetin, rutin, herbacetin 3,7-O-dimethyl ether and its aglycone herbacetin, gallocatechin and its derivatives, catechin gallocatechin), chromones (8-[C-β-D-[2-*O*-(*E*)-cinnamoyl] glucopyranosyl]-2[(R)-2-hydroxypropyl]-7-methoxy-5- methylchromone, 8-*C*-β-*D*-[2-*O*-(*E*)-coumaroyl]glucopyranosyl-2-[2-hydroxy]propyl-7-methoxy-5-methylchromone, isorabaichromone, aloesin, aloeresin A, aloeresin B), coumarins (dihydrocoumarin and dihydrocoumarin ethyl ester, umbelliferone), anthraquinones (aloin, emodin, aloe emodin), hydrolyzable tannins such as ellagitannins (oenothein B, eugeniflorin D2, tellimagrandins I and II, punicalagin, punicalin, pedunculagin, strictinin A, granatins A and B, casuarinin, corilagin, gallagyldilacton), caroboxylic acid (cinnamic acid), tetrahydroxy-cyclohexane carboxylic acid (quinic acid 3,5-di-O-gallate), terpenoids (monoterpenoids (carvacrol, thymol), sesquiterpenoids (α-bisabolol, (-)-α-bisabololoxides A and B, chamazulene, chamaviolin, en-yn-dicycloethers, farnesene, farnesol, matricin, nerolidol), fatty acids (α-linolenic acid, linoleic acid, oleic acid, palmitoleic acid, palmitic acid, and stearic acid), saponins, sterols, proteins, peptides, hormones, enzymes, and vitamins (Table 2). Several studies have revealed the beneficial role of phytochemicals in wound healing. The role of various polysaccharides in the healing of wounds and burns, via their immunomodulatory effects, antioxidant properties, macrophage activation, controlling the inflammatory responses, stimulating wound contraction, accelerating the phases of re-epithelialization and remodelling, has been demonstrated in a number of studies [118,271-274]. Phenolics derived from various natural sources are linked to antioxidant, anti-inflammatory, antiallergic, anticarcinogenic, antihypertensive, cardioprotective, anti-arthritic and antimicrobial activities. The antioxidant activity of phenolics is primarily attributed to their redox properties that enable them to act as singlet oxygen quenchers, reducing agents and their hydroxyl (-OH) groups are good H-donating antioxidant agents that disrupt the cycle of new radical generation by scavenging reactive oxygen species. Various studies validated the positive correlation between phenolic content and the antioxidant activity [275]. Positive correlation between the antioxidant activity and phenolic content was also observed by the extracts of *A. vera* leaves [22,47], *C. recutita* flowers [100,102], *M. communis* leaves [162,163,184], and *P. granatum* peel [201,203,212,213,215,216,276]. For *R. nervosus* leaves, a correlation was observed between the principal polyphenolic components (flavonols) of the extract and the antioxidant activity [244] (Table 2; Supplementary material, Table S1). The inhibitory effects of polyphenolic compounds against bacterial

pathogens have been ascribed to their ability to attack several targets of pathogenic microorganisms such as the inhibition of nucleic acid synthesis, the perturbation of the cytoplasmatic membrane and thereby affecting the permeability and leading to intracellular constituent release and the inhibition of energetic metabolism and thus interfering with membrane functions such as electron transport, nutrient absorption, nucleic acid synthesis, and ATPase activity [277]. Although the precise mechanisms of the anti-inflammatory activity of phenolic compounds are not fully elucidated, it is has been hypothesized that phenolic compounds exert anti-inflammatory activity by inhibition the synthesis of pro-inflammatory mediators, modification of eicosanoid synthesis, inhibition of activated immune cells, or inhibition of nitric oxide synthase and COX-2 via the inhibitory effects on nuclear factor NF-κβ [278]. Several monoterpenoids including thymol were shown to accelerate wound healing via their anti-inflammtory, antioxidant, and antimicrobial activities as well as modulation of some wound healing phases [279]. *In vivo* and *in vitro* experimental studies have indicated the potential anti-inflammatory activity of sesquiterpenes via modulating or suppressing elements that play a direct role in the inflammatory response [280]. Saponins are effective in wound healing due to their antioxidant and antimicrobial activities, which appear to play a role in wound contraction and elevated rate of epithelialization [8]. Phytosterols were reported to possess antioxidant and antimicrobial activities [281-284]. The role of vitamins in accelereating wound healing due to their antioxidant, anti-inflammatory and immunomodulatory activities as well as their stimulatory effects on various phases of tissue healing has been evaluated in several studies [285,286].

The knowledge of the side effects and/or risks associated with the use of herbal and non-herbal remedies is very crucial in order to promote awareness among herbalists, health professionals and the public on the risks associated with excessive or chronic use of herbs. *Aloe vera* gel topical application has been reported to cause a number of side effets such as contact and photodermatitis and/or erythema with papulous, acute skin rash, burning sensation in some patients, and mild itching. All adverse effects were reversible and *Aloe vera* was generally well tolerated [28,70]. Chamomile is considered safe to use topically and orally and is included in the FDA (Food and Drug Administration, USA) GRAS (generally recognized as safe) list [287,288]. However, both oral and topical uses of chamomile flowers have been reported to cause contact dermatitis, particularly among those who also have allergies to other plants in the daisy family (Asteraceae or Compositae) [89,287,288]. The tragacanth gum is also considered as GRAS and approved as a food ingredient (emulsifier, stabilizer, thickener and gelling agent) by the FDA, and by the European Union and has been accorded with E413, a European food safety E number [289]. Honey poses a small risk of wound infection as it may contain some clostridial spores. However, this risk can be reduced by using honey treated with gamma-irradiation, which can kill the spores while maintaining honey's antibacterial activity. On the other hand, there has not been a single occurrence of wound infection contributed by clostridial spores with the topical application of honey in approximately 2000 cases reported in 2014. Although there may be some toxic effects from the ingestion of poorly handled honey, there have not been any documented toxic effects associated with the topical application of honey on diabetic wounds in comparison with the risk of using other conventional wound healing therapies. Besides these few limitations, many studies reported honey as a non-toxic, non-allergenic, non-irritating healing agent with no cytotoxic effects; it is a safe, cheap, and effective healing agent [131]. Potassium alum is considered by the FDA as GRAS substance. It is used in different products like food or drugs as buffer, neutralizing or forming agent [290]. Furthermore, we did not find any report on possible side effects following the topical use of cuttlefish bone, *L. usitatissimum* seeds oil, *M. bengalensis* leaves, *M. communis* leaves, *P. granatum* pericarp, *R. nervosus* leaves, and *T. laevigatus* leaves. Consequently, the herbal and non-herbal remedies used in Sana'a for the treatment of wounds and burn can be considered generally safe upon a proper usage in quantity and manner.

CONCLUSION

This work provides scientific data on the pharmacological activities (anti-inflammatory, antioxidant, antimicrobial and wound healing activities) of twelve herbal and non-herbal remedies that could justify the claimed usefulness of these remedies for their traditional use in Sana'a for the treatment of wounds and burns. This study opens the opportunities for further evaluation of the effectiveness and safety of the remedy's raw materials and determination of the rational way of their using either as a single use and/or in combinations. Moreover, further research of the raw materials and their associated active compounds is needed to develop useful alternatives for wound healing.

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COMPETING INTERESTS

The authors declare no conflict of interest.

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Table S1: Antioxidant mechanisms of action of the raw materials, extracts and active chemical constituents of the herbal and non-herbal remedies used in Sana'a for the treatment of wounds and burns

Raw materials, extracts, and active chemical constituents	Antioxidant mechanisms of action
Aloe vera leaves	
Gel	• Scavenging 1,1diphenyl-2-picrylhydrazyl (DPPH•), and 2,2´-azino-bis(3-ethylbenzo-thiazoline-6-sulfonic acid ($ABTS^{+\bullet}$) free radicals and NO with IC_{50} values of 572.14 ± 2.21 μg/ml, 105.26 ± 0.22 μg/ml and 46.36 ± 1.35 μg/ml, respectively [45]. • Increasing superoxide dismutase (SOD) activity and decreasing the lipid peroxidation products in diabetic rats [43].
Ethanol extract of the gel	• Reverting back the increased levels of lipid peroxidation and hydroperoxides in tissues of diabetic rats to near normal levels and increasing the reduced glutathione (GSH), SOD, catalase (CAT), glutathione peroxidase (GPx) and glutathione-S-transferase (GST) in the liver and kidney of diabetic rats significantly [42]. • Normalizing the azoxymethane-induced reduction in hepatic GSH and uric acid, and significant increasing the hepatic CAT, SOD and glucose-6-phosphate dehydrogenase activities as well as recovering the azoxymethane-induced decline in colonic GSH-peroxidase, glucose-6-phosphate dehydrogenase and GST [44].
Aqueous extract of leaves (without the gel)	• Inhibitory capacity against Fe3+/ascorbic acid induced phosphatidylcholine liposome oxidation, scavenging DPPH•, $ABTS^{\bullet+}$ and superoxide anion ($O_2^{\bullet-}$) radicals and acting as reductant [46].
Chloroform-ethanol (1/1), ethyl acetate, hexane extracts of leaf skin.	• Chloroform-ethanol (1/1) extract reduced DPPH• (IC_{50} = 0.274 mg/ml), followed by the ethyl acetate extract (IC_{50} = 0.326 mg/ml) and the hexane extract (IC_{50} = 0.366 mg/ml) comparing to the reference substances butylated hydroxytoluene (BHT) and α-tocopherol (IC_{50} = 69 μg/ml and 7.5 μg/ml, respectively) [22].
Methanolic extract of leaf skin.	• Scavenging DPPH• radicals (58.8% ± 0.4) and showing ferric reducing antioxidant power activity (2.4 mmol ± 0.1) [47].
Dihydrocoumarin and dihydrocoumarin ethyl ester from the sap	• Scavenging $O_2^{\bullet-}$ and hydroxyl •OH radicals by dihydrocoumarin (29.83% and 43.67%, respectively) and by dihydrocoumarin ethyl ester (230.33% and 42.33%, respectively) [51].
8-C-*β-D*-[2-*O*-(*E*)-coumaroyl] gluco-pyranosyl-2-[2-hydroxy] propyl-7-methoxy-5-methyl-chromone from methanolic extract of the gel.	• Suppression of peroxidation (using the rat brain homogenate peroxidation system) at 0.15 μM, which was comparable to that α-tocopherol (0.15 μM) [50].
Isorabaichromone, aloeresin B, aloesin and aloeresin A	Isorabaichromone [34] • A potent inhibitory of the production of lipid peroxides induced by microsomal NADPH-oxidation with IC_{50} value of 23 μM compared to that of the reference compounds quercetin and catechin (IC_{50} values of 21.8 and 14.5 μM, respectively). • A potent DPPH• radical scavenger with IC_{50} value of 4 μM followed by the compounds aloesin, aloeresin A and aloresin B with IC_{50} values of 20 μM, 26 μM and 26 μM, respectively comparing to that of α-tocopherol, quercetin and catechin (IC_{50} values of 14 μM, 3 μM and 4.3 μM, respectively). • The effective compound in scavenging $O_2^{\bullet-}$ generated by xanthine/xanthine oxidase system with IC_{50} value of 7 μM comparing to that of quercetin (IC_{50}= 53.8 μM) and catechin (IC_{50}= 0.8 μM). • Completely inhibition of ascorbic acid-dependent mitochondrial lipid peroxidation at IC_{50} value of 30μM, while aloeresin B showed protection against lipid peroxidation with an IC_{50} value of 95 μM comparing to that of quercetin and catechin (IC_{50} values of 13.4 μM and 12.7 μM, respectively). Aloeresin B [34] • Inhibitory of the lipid peroxides in ascorbic acid-dependent microsomal lipid peroxidation with IC_{50} value of 85 μM compared to that of α-tocopherol, quercetin and catechin (IC_{50} values of 98 μM, 19 μM and 29.3 μM, respectively).
Several polysaccharides, APS from the gel, APS- 1 from *Aloe vera var. chinensis leaves*, APS from *Aloe vera* gel, GAPS- 1 and SAPS- 1 (from the gel and the skin).	APS-1 [52] • Scavenging $O_2^{\bullet-}$ radicals with IC_{50} value of 22 μg/ml (ca. 0.1μmol/l). • Scavenging activity at 100μg/ml against •OH in site-specific and site non-specific assays was 66.8% and 47.4%, respectively. • Inhibiting significantly the Cu^{2+}-induced lipid peroxidation in human LDL. The protection capacities at 50,70,100, and 120 μg/ml were 9.4%, 24.1%, 39.2% and 54.8%, respectively. • The pre-incubation of PC-12 cells (pheochromocytoma cell line) with APS-1(300 μg/ml) attenuated in a dose-dependent manner the increase in the malondialdehyde (MDA) level and in the lactate dehydrogenase (LDH) activity of the H_2O_2-injured cells by 46% and 52%, respectively ($p<0.05$). Moreover, it recovered the H_2O_2-decreased GPx, CAT and SOD activities to over 63%, which was higher than those done by the positive reference, vitamin E at 1 mM. APS [54] • Scavenging activity of DPPH•, •OH and alkyl radicals with IC_{50} values of 0.67 mg/ml, 0.66 mg/ml and 0.15 mg/ml, respectively. • Reduction in the levels of reactive oxygen species in Vero cells subjected to 2,2-azobis(2-amidinopropane) hydrochloride (AAPH)-induced oxidative stress and increase in the reduced cell viabilitiy of AAPH-treated Vero cells.

(*Contd...*)

Table S1: *(Continued)*

Raw materials, extracts, and active chemical constituents	Antioxidant mechanisms of action
	• In the *in vivo* AAPH-induced oxidative stressed zebrafish model, the survivl rates of APS-treated group (50, and 100 μg/mL) was 100%.
	GAPS-1 and SAPS-1 [53]
	• Strong scavenging activities against $O_2^{\bullet-}$ (IC_{50} values of 1.9 mg/mL and 2.8 mg/mL, respectively) comparing to the reference substance, ascorbic acid with IC_{50} = 0.8 mg/mL.
	• Moderate ferrous chelating effect (38.1% and 32.2%, respectively) at the concentration of 8mg/mL, whereas ascorbic acid had low ferrous chelation throughout the test.
	• Moderate scavenging activity of •OH radical (51.4% and 35.7%, respectively) at the concentration of 8mg/mL comparing to ascorbic acid (58% inhibtion at 1.0mg/mL).
	• Moderate reductive power (using the potassium ferricyanide reduction method). At the concentration exceeded 0.1 mg mL-1, reductive power of GAPS-1 was significantly higher ($P < 0.05$) than that of SAPS-1.
	• Moderate inhibition of lipid peroxidation: (42.6% and 46.2%, respectively) at a concentration of 8.0 mg/mL, comparing to that of ascorbic acid (73.8% at 2mg/mL).
	• GAPS-1 showed moderate scavenging activity of hydrogen peroxide (IC_{50} = 4.2mg/mL), while SAPS-1 exhibited weak scavenging activity of hydrogen peroxide.
Aloe-emodin	• Protective effects against carbon tetrachloride-induced lipid peroxidation in rat liver [31].
	• Inhibitory activity against peroxidation of linoleic acid, catalyzed by soybean 15-lipoxygenase, with IC_{50} value of 65 ± 3 μmol/l [48].
	• 78% Inhibition of peroxidation of linoleic acid as well as scavenging activity (16.6 %) of •OH radicals at a concentration of 0.25 mg/ml [49].
Glycoprotein (m.w. 14 kDa)	• Scavenging activity (IC_{50} = 21.4 ± 1.4 μM) against $O_2^{\bullet-}$ generated by the xanthine-xanthine oxidase [36].
***Chamomilla recutita* flowers**	
Extracts	Methanolic extract
	• DPPH• radical scavenging activity (EC_{50} = 0.0022 ± 0.0005) with antiradical power ($1/EC_{50}$) of 455 ± 35.7) [100].
	Water extract of ligulate flowers obtained by subcritical water extraction
	• DPPH• radical scavenging activity (IC_{50} = 0.0211 mg/mL) and ferric reducing power activity (EC_{50} = 0.578 mg/mL) [102].
	70% ethanolic extract
	• DPPH• radical scavenging activity (IC_{50} = 0.152 mg/mL) [97].
	Dichloromethane extract of the distillate
	• In the aldehyde/carboxylic acid assay, the highest dose (500 μg/ mL) inhibited hexanal oxidation by 50% over a 40 day period comparing to the standard substances BHT (99% inhibition at 10 μg/ mL) and α tocopherol (89% inhibition at 10 μg/ mL). In conjugated diene assay, the inhibitory effect toward methyl linoleate oxidation (without initiators or metal catalysts) was 31% at 200 μg/mL comparing to BHT and α-tocopherol (100% and 99% inhibition at 10 μg/mL, respectively) [96].
	Ethyl alcohol-water (1:1) extract
	• DPPH• radical scavenging activity (EC_{50} = 5.52 ± 0.15 mg/ml). The reduction of lipid peroxidation in sunflower oil after 32 days, monitored as lipid peroxide number (meq O_2/kg oil) and thiobarbituric acid number (meq MDA /kg oil), of 1 mg/ml extract was 44.20 ± 0.24 and 0.230 ± 0.00, respectively comparing to the control (without antioxidant) (78.76 ± 0.35 and 0.586 ± 0.02, respectively) [99]
	Water, ethanol and methanol extracts
	• The iron sulfate-, sodium nitroprusside- and 3-nitropropionic acid-induced TBARS (thiobarbituric acid reactive substance, a byproduct of lipid peroxidation) production in rat brain were significantly inhibited by water extract (IC_{50} values of 848.9 ± 169.8 μg/ml; 58.4 ± 4.7 μg/ml and 202 ± 31.5 μg/ml, respectively), ethanol extract (IC_{50} values of 1874.3 ± 691 μg/ml; 826.3 ± 70.3 μg/ml and 1107.4 ± 49.4 μg/ml, respectively) and methanol extract (IC_{50} values of 415 ± 14.2 μg/ml; 299.2 ± 8.1 μg/ml and 590.9 ± 25.5 μg/ml, respectively). The inhibitory potency of DPPH• radical was in the following order: methanol (IC_{50} = 115.9 ± 16.3 μg/ml) > ethanol (IC_{50} = 258.9 ± 13.3 μg/ml) >water (IC_{50} = 947.2 ± 22.5 μg/ml) ($P < 0.01$) [98].
Essential oil	• Moderate DPPH• scavenging activity in a concentration dependent manner reaching an inhibition of 80.35% with the highest concentration (500 mg/mL) comparing to 65.81% inhibition by the reference substance (1 mg/mL of α-tocopherol). It also inhibited the oxidation of linoleic acid (The maximum inhibition of 92.1% and 91% was observed at 96 h with 140 mg/mL and 280 mg/mL of essential oil, respectively [103].
	• DPPH• radical scavenging activity (IC_{50} = 2.20 mg/mL) comparing to ascorbic acid (reference) with IC_{50} value of 0.015 mg/mL [266].

(*Contd...*)

Table S1: *(Continued)*

Raw materials, extracts, and active chemical constituents	Antioxidant mechanisms of action
70% Aqueous methanol extract and its content of apigenin-7-O-(6″-acetyl)-glucoside, luteolin, apigenin, eupatolitin, and chrysosplenol D	• $DPPH^{\bullet}$ scavenging activity with an SC_{50} value (the concentration of sample required to scavenge 50% $DPPH^{\bullet}$ radicals) of 3.06 ± 0.09 mg/mL comparing to ascorbic acid (reference) with SC_{50} value of 0.42 ± 0.04 mg/mL. Reduction of the peak areas of the flavonoids (apigenin-7-O-(6″-acetyl)-glucoside, luteolin, apigenin, eupatolitin, and chrysosplenol D) in the chromatogram of the sample extract solution treated with $DPPH^{\bullet}$ comparing to those in the chromatogram of sample extract solution without $DPPH^{\bullet}$ treatment indicated that the five flavonoids played an important role in the antioxidant activity of the extract solution [101].
Polyphenolic-polysaccharide conjugates	• Scavenging activity of $DPPH^{\bullet}$ and $ABTS^{+\bullet}$ with EC_{50} values of ≈ 100 μg/mL and 8.45 μg/mL, respectively comparing to the reference compound (Trolox) with EC_{50} values of 3.22 and 2.24 μg/mL, respectively. Pre-incubation of blood plasma with polyphenolic-polysaccharide conjugates considerabley diminished significantly the extent of $ONOO^{-}$-induced oxidative stress of the biomarkers of blood plasma protiens such as protein carbonyl (at the concentrations of 0.5,100 and 300 μg/mL) and thiol groups (at the concentrations of 5-300 μg/mL) , nitrated proteins (3-nitrotyrosine at the concentrations of 5 and100-300 μg/mL), and the formation of lipid hydroperoxides in plasma samples (at the concentrations of 0.5-50 and 200-300 μg/mL). Moreover, the ferric reducing ability of blood plasma was increased in the pesence of the conjugates (at the concentrations of 5, 200 and 300 μg/mL) [108].
α-Bisabolol	• Inhibition of the upregulation of H_2O_2-generated free radicals in human skin fibroblasts *in vitro* [105]. • Significant inhibition of reactive oxygen species production during human polymorphonuclear neutrophil bursts induced by *C. albicans* and N-formyl-methionyl-leucylphenylalanine at concentrations ranging from 7.7 to 31μg/ml and 3.8 to 31μg/ml, respectively. A similar effect of α-bisabolol at concentration ranging from 3.8 to 31 μg/ml was observed in the cell-free systems (SIN-1 and H_2O_2/$HOCl^{-}$ systems) [104].
Chamazulene	• $DPPH^{\bullet}$ radical scavenging activity (IC_{50} = 0.27 mg/mL) comparing to ascorbic acid (reference) with IC_{50} value of 0.015 mg/mL [266]. • Inhibition of Fe^{2+}/ ascorbate-induced lipid peroxidation (50% inhibition with 18 μM after 45 min incubation). In the same study, chamazulene (25 mM) was also shown to inhibit the autoxidation of dimethyl sulfoxide (DMSO) (33 mM) by 76% and had a weak capacity to interact with $DPPH^{\bullet}$ radicals [89].
α-Bisabolol and chamazulene	• The most effective antioxidants according to HPTLC-$DPPH^{\bullet}$ assay of the supercritical CO_2 extract [106].
α-Bisabolol oxide A and (E)-β-farnesene	• $DPPH^{\bullet}$ radical scavenging activity with IC_{50} values of 1.50 mg/mL and 7.45 mg/mL, respectively comparing to ascorbic acid (reference) with IC_{50}value of 0.015 mg/mL [266].
Cuttlefish bone	
Polysaccharides with a total sugar content of 86.2% extracted from the cuttlebone of *Sepia aculeate*.	• The $DPPH^{\bullet}$, $O_2^{\bullet-}$ and $^{\bullet}OH$ radical scavenging activities were found to be 36.27% at 10 mg/ml, 59.57% at 0.5 mg/ml and 45.86% at 3.2 mg/ml, respectively, comparing to the reference substances, BHT, and α-tocopherol (86.38 and 90.96% at 10 mg/ml, 88.41 and 78.23% at 0.5 mg/ml, and 84.36% and 72.40%, at 3.2 mg/ml, respectively). The ferrous ion-chelating effect of polysaccharides was 48.61% at 10 mg/ml, comparing to positive control, ethylenediaminetetraacetic acid (EDTA) (95.52% at 10 mg/ml) [124].
Cuttlefish bone (CB) ointment (CB extract: white petroleum 4:6)	• CB (0.5 g/cm2) treatment decreased MDA activity levels (indicating inhibition of lipid peroxidation) 96 h after burn. MDA activity in the CB-treated rats (6.32 ± 0.46) was similar to that of the silver sulfadiazine (0.5 g) treated rats (5.56 ± 0.51) comparing to that of the nontreated group (9.79 ± 0.3) [122].
Honey	
Honey	• In a single-blind prospective randomized control study involving patients with partial-thickness burns ranging from 5-30% total body surface area, Honey treatment led to a decline in the levels of serum lipid peroxide during 21 days (from 6.25 to 2.21 nmol/ml) comparing to silver sulfadiazine (from 6.42 to 3.90 nmol/ml). The rate of increase in serum ceruloplasmin levels was relatively slow during honey treatment and there was no significant effect on serum uric acid levels in comparison with patients treated with silver sulfadiazine [132].
Linum usitatissimum **seed oil**	
Flaxseed hull oil	• $DPPH^{\bullet}$ scavenging activity (ca 65%)[143].
Meriandra bengalensis **leaves**	
Essential oil from Yemeni *M. bengalensis* leaves	• Exhibited very weak $DPPH^{\bullet}$ scavenging activity with an IC_{50} of 35 μg/mL comparing to the positive control, ascorbic acid (6.2 ± 0.5 μg/mL) [151].
Myrtus communis **leaves**	
Extracts	<u>Aqueous, total flavonoid oligomers, ethyl acetate and methanol extracts</u> • $DPPH^{\bullet}$ scavenging activity with IC_{50} of 1.9 μg/ml, 3 μg/ml, 5.2 μg/ml and 6.5 μg/ml, respectively comparing to positive control α-tocopherol (IC_{50} = 3.1 μg/ml) [161]. <u>Methanol, ethanol and water leaf extracts</u> • $DPPH^{\bullet}$ scavenging activity ranged from 46.7% to 49.8% at 50 μg/mL comparing to both standard substances, ascorbic acid and Trolox, which showed 96.9% radical scavenging activity at 50 μg/mL. The water extract showed the strongest ferric reducing power and was even more effective than the reference BHT at some concentrations (250 and 500 μg/mL). Methanol extract also showed strong activity. The antioxidant activity evaluated by β-carotene linoleic model system was 94.0% for methanol followed by the water 87.4%, and ethanol 86.5% extracts at 2g/L. [163]. <u>Methanolic extract</u> • $DPPH^{\bullet}$ scavenging activity with IC_{50} value of 9.54 mg/l comparing to ascorbic acid (reference) with IC_{50} value of 0.51 mg/l. The total antioxidant capacity determined as ferric reducing power was 70.2 mmol Fe^{2+}/l [162].

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Table S1: *(Continued)*

Raw materials, extracts, and active chemical constituents	Antioxidant mechanisms of action
	70% Ethanolic extract, and its fractions (ethylacetate and aqueous extracts) obtained by liquid-liquid extraction • Inhibition of lipid peroxidation and diene-formation induced by copper ions in human low-density lipoprotein with IC_{50} values of 0.36 μM, 2.27 μM and 2.88 μM, respectively [160]. 80% Ethanolic extract • Higher DPPH$^{\bullet}$ scavenging activity with IC_{50} = 4.17±1.06 μg/mL comparing to the standard substance BHT with IC_{50} value of 66.6 ± 10.30 μg/mL. The antioxidant activity using ferric reducing antioxidant power (FRAP) assay was 0.260 ± 0.011 at 30 μg/mL [156]. Methanolic extract of *M. communis* var. *italica* L. • Higher DPPH$^{\bullet}$ scavenging activity (IC_{50} = 8 μg/ml) and ferric reducing power (EC_{50} = 10 μg/ml) than positive controls BHT (IC50 = 25 μg/ml) and ascorbic acid (EC_{50} = 40 μg/ml), respectively. The lipid peroxidation activity assessed by β-carotene-linoleate bleaching method was similar to that of BHT (IC_{50} of 70 μg/ml). The chelating ability was very low (IC_{50} = 5 mg/ml) comparing to the positive control EDTA (IC_{50} = 0.03 mg/ml) [164].
Essential oil	• The lipid peroxidation activity assessed by β-carotene-linoleate bleaching method was 42.98% comparing to the positive controls *Thymus x-porlock* 77.34% and BHA 86.75% [165].
Semi-myrtucommulone and myrtucommulone A	• Both semimyrtucommulone and myrtucommulone A were active but signifcant differences in their effcacy were observed, with semimyrtucommulone showing superior antioxidant activity in all systems, and neither compound showing pro-oxidant activity. During the autoxidation of linoleic acid, semimyrtucommulone exerted a signifcant antioxidant activity (IC_{50} of 2.9 nmol), comparable to that of α-tocopherol (IC_{50} of 1.7 nmol). In the test of iron-catalyzed oxidation of linoleic acid, semimyrtucommulone was even more potent ($IC_{50}$of 15.4 nmol) than α-tocopherol (IC_{50} of 27.5 nmol). In addition, semimyrtucommulone could signifcantly inhibit ferric-nitrilotriacetate induced fatty acids peroxidation (in rat liver homogenates) in a dose dependent manner. The protection level exceeds 50% at a concentration of 50μM, and the fatty acids oxidation is almost completely inhibited at a concentration of 500μM. Moreover, semimyrtucommulone (tested concentrations 1.25-10 μM) inhibited lipid peroxidation induced by 750μM tert-butyl hydroperoxide or 200μM FeCl3 on human embryonic lung fibroblasts cells from a concentration of 2.5μM and 1.25 μM, respectively [166]. • During the thermal (140°C), solvent-free oxidation of cholesterol, both semimyrtucommulone and myrtucommulone A showed great efficiency in protecting cholesterol against oxidative degradation, with an IA_{50} (amount of antioxidant that gives a protection of 50% of the cholesterol decrease during oxidation) values of < 2.5 nmol and 3.15 nmol at 1h, 5 nmol and 8nmol at 2h, for myrtucommulone A and semimyrtucommulone, respectively, comparing to vitamin E (natural antioxidant) with IA_{50} value of < 0.5nmol and 0.7nmol at 1h and 2h, respectively. Moreover, the pretreatment with semimyrtucommulone and myrtucommulone A significantly preserved LDL from oxidative damage induced by Cu^{2+} ions at 2 h of oxidation, and showed remarkable protective effect on the reduction of polyunsaturated fatty acids and cholesterol, inhibiting the increase of their oxidative products (conjugated dienes fatty acids hydroperoxides, 7β-hydroxycholesterol, and 7-ketocholesterol [167].
Myricetin-3-0 galactoside and myricetin-3-0-rhamnoside from *M. communis var italica*	• Inhibition of lipid peroxidation with IC_{50} values of 160 μg/ml and 220 μg /ml by myricetin-3-0-galactoside and myricetin-3-0-rhamnoside, respectively. The two compounds showed the most potent inhibitory effect of xanthine oxidase activity (and their effect on the $O_2^{\bullet-}$ enzymatically generated in this system) by respectively, 57% and 59% at a concentration of 100 μg/ml. The IC_{50} values for the DPPH$^{\bullet}$ radical scavenging activities of both compounds were 2.3 μg /ml and 1.4 μg/ml, respectively comparing to the positive control (vitamin E with IC_{50} value of 3μg /ml) [169].
Four hydrolysable tannins [oenothein B , eugeniforin D2 , and tellimagrandins I and II], two related polyphenolic compounds [gallic acid and quinic acid 3,5-di-0-gallate], and four myricetin glycosides (myricetin 3-0-β-D-xyloside, myricetin 3-0-β-D-galactoside, myricetin 3-0-β-D-galactoside 6″-0-gallate, and myricetin 3-0-α-L-rhamnoside	• Among the tested compounds, the four hydrolysable tannins oenothein B, eugeniflorin D2, and tellimagrandins I and II exhibited potent DPPH$^{\bullet}$ radical scavenging activity (EC_{50} 6.12 μM, 4.56 μM, 8.00 μM and 7.62 μM, respectively) [168].
***Punica granatum* L. fruit peel**	
Extracts	Methanol extract • showed 83% and 81% antioxidant activity at 50 ppm using the β-carotene-linoleate and DPPH$^{\bullet}$ model systems, respectively. At 100 ppm, the methanol extract showed 56% inhibition of lipid peroxidation, 58% $^{\bullet}$OH radical scavenging activity, and 93.7% antioxidant effect against LDL oxidation [201].

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Table S1: *(Continued)*

Raw materials, extracts, and active chemical constituents	Antioxidant mechanisms of action
	• Among different extracts, methanol extract exhibited maximum significant DPPH• and NO radical scavenging activity with IC_{50} value of 24.43 μg/ml and 45.56 μg/ml, respectively compared to standard antioxidant ascorbic acid (IC_{50} = 11.16 μg/ml and 27.70 μg/ml, respectively) [196]. • Treatment of rats with a single dose of CCl4 at 2.0 g/kg of body weight decreases the levels of CAT, SOD, and peroxidase by 81, 49, and 89% respectively, whereas the lipid peroxidation value increased nearly 3-fold. Pretreatment of the rats with a methanolic extract of pomegranate peel at 50 mg/kg (in terms of catechin equivalents) followed by CCl4 treatment causes preservation of CAT, peroxidase, and SOD to values comparable with control values, whereas lipid peroxidation was brought back by 54% as compared to control. Histopathological studies of the liver of different groups also support the protective effects of the MeOH extract by restoring the normal hepatic architecture [202]. 50% Aqueous methanol extract • Administration to rats induced a significant reduction in MDA of liver and kidney (52 and 36%, respectively). The extract was also able to significantly decrease the NO level in hepatic and renal tissues by 12% and 48%, respectively. The extract induced a significant increase in CAT level (1.52 ± 0.01U/g) compared to the control (1.51 ± 0.02 U/g) in the renal tissues. There was a significant increase in the level of SOD in the hepatic tissue (1.75 ± 0.01 U/g) when compared to the control group (1.06 ± 0.01 U/g). The level of SOD was significantly increased by about 4 folds in the renal tissue (2.89 ± 0.01U/g) compared to the control (0.74 ± 0.01U/g). Glutathione reductase (GR) was not altered in hepatic tissue while in the renal tissues the level was significantly reduced (13.73 ± 7.86 μmol/g) comparing to the control (15.87 ± 3.07 μmol/g). Renal GPx was significantly increased (1589.94 ± 85.49 U/g) when compared to the control group (1125.77 ± 83.03 U/g). The extract did not affect GST in hepatic tissue of rats although it has been decreased significantly in the renal tissues (0.51 ± 0.03 μmol/h/g) comparing to control (0.65 ± 0.02 μmol/h/g) [211]. 75% Aqueous methanolic extract • The $ABTS^{\bullet+}$ radical scavenging activity at the amount of (50-250μg) was significantly higher than quercetin ($p \geq 0.05$, at least) and as strong as standard compound (BHA). In addition, the antioxidant activity of the extract at 500ppm evaluated by β-carotene linoleic model system was more than 75%, which is as strong as the synthetic antioxidants Trolox and BHA [210]. Ethanol extract • DPPH• radical scavenging activity of 92.38% at the concentration of 35 μg/mL, which is almost equivalent to that of the standard substance BHA (93.59 %) at the same concentration. At the concentration of 700 μg/mL, it exhibited a ferric reducing power of 1.40 Abs at 700nm [215]. • 58% antioxidant activity measured by β-carotene bleaching test [216]. • DPPH• radical scavenging activity (IC_{50} value of 0.003 mg/ml) and the Trolox equivalent antioxidant capacity value from ABTS assay was 4.066 mM/mg [206]. Ethyl acetate extract • 2-10 μg/mL showed a total antioxidant capacity (cupric (Cu^{2+}) reducing power) ranged from 42.3 - 461.2 μmol Trolox equivalent/ g dry solids [212]. Methanol, acetone, ethanol and chloroform extracts • The percent inhibition of linoleic acid peroxidation was 92.69 ± 6.31, 91.04 ± 9.20, 89.23 ± 4.27 and 80.22 ± 7.08, respectively [207]. Methanol and water extracts • DPPH antioxidant activities were 4081.43 and 3497.02 mmol Trolox/g, respectively) [217]. Methanol, ethanol, acetone and ethyl acetate fractions [208] The antioxidant activity of the fractions measured by four *in vitro* assays were: • Total antioxidant activity measured at the concentration of 80μg/mL by phosphomolybdenum: Methanol fraction showed the highest antioxidant activity (5067.7μmol) followed by ethanol (3323.0μmol), acetone (2481.6μmol), and ethyl acetate fractions (862.86 μmol). • The DPPH• scavenging activity of the fractions were: methanol fraction (90.53%), acetone fraction (86.4%) and ethanol fraction (83.2%) comparing to that of the positive controls, ascorbic acid and BHT (91.1% and 85.6, respectively). • The fractions had effective reducing power using potassium ferricyanide reduction method and cupric reducing antioxidant capacity assay with methanol fraction as the most active one followed by ethanol, acetone, and ethyl acetate fractions. The results were comparable to ascorbic acid and BHT. Ethyl acetate, acetone, methanol and water extracts • The different extracts (at 25, 50, 75 and 100 μg/ml) exhibited various degrees of antioxidant capacity. The highest antioxidant capacity (expressed as equivalents of ascorbic acid (μmol/g of extract)) was observed in methanol extract (708 ± 1.35 and 2457 ± 56.3 μmol at 25 and 100 mg/ml concentrations, respectively). Acetone extract (50 μg/ml) and ethyl acetate (75 μg/ml) extract showed strong antioxidant capacities (1392 ± 69.0 and 1935 ± 99.4 μmol, respectively) as well. The water extract showed the lowest antioxidant capacity [203]. Peel extracted by a mixture of methanol, ethanol, acetone and water: • showed higher FRAP than that of the pulp. At 50 g/l, the scavenging capacity against $O_2^{\bullet-}$ was 43.0%, higher than that of the pulp (37.7%). It possessed a higher capacity against •OH and peroxyl radicals as well as inhibiting CuSO4-induced LDL oxidation than the pulp extract [204]. Peel extracts (a mixture of methanol, ethanol, acetone and water extracts) of two Iranian pomegranate cultivars (Malas-Saveh and Aghamohammadali)

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Table S1: *(Continued)*

Raw materials, extracts, and active chemical constituents	Antioxidant mechanisms of action
	• showed concentration (25-100μg/mL) dependent increase in the antioxidant capacity (903-2743 and 1002-2887μmol g-1 of extract) (expressed as ascorbic acid equivalent) (determined by the formation of phosphomolybdenum complex) [205]. Ellagic acid rich extract: • DPPH$^{\bullet}$ scavenging activity (ED_{50} = 14.91 μg/mL) comparing to standard quercetin (ED_{50} = 3.57 μg/mL) [209].
Punicalagin	• The DPPH$^{\bullet}$ radical scavenging activity of commercial standard punicalagin and the reference substances Trolox and BHT at the concentration of 0.1 mg/ml was 23.9% 66% and 24%, respectively. The percent of H_2O_2 scavenging activity was 17.8%, 19%, 13%, respectively. Ferrous chelating activity of punicalagin (0.1mg/ml) was 18% comparing to the standard substance, (EDTA) (0.1mg/ml) with 97%. The ferric reducing activity of punicalagin increased in a dose dependent manner [222]. • The ABTS$^{\bullet}$- radical scavenging activity was nearly half that of the antioxidant reference substances, n-propyl gallate, and Trolox-c. The ABTS$^{\bullet-}$, guanosine, and tryptophan radical generated by pulse radiolysis were repaired by punicalagin by electron transfer. The IC_{50} value of punicalagin for inhibition of lipid peroxidation was 36.8 ± 0.6 μg/mL in comparison to an IC_{50} value of ~86.32 ± 1.5 μg/mL for the reference substance (BHA). Binding of punicalagin with bovine serum albumin and metal ions such as iron and copper revealed different binding affinities, whereas its binding with DNA was very weak and nonspecific [221].
Punicalagin, punicallin and ellagic acid	• The *in vitro* antioxidant activity trends were ellagic acid (EA)> punicalagin (PG)> punicallin (PL)>Trolox (reference) in scavenging DPPH$^{\bullet}$ radicals, PG>PL>EA≈Trolox in scavenging $O_2^{\bullet-}$, EA>PG≈PL>Trolox in FRAP, and Trolox>PG>EA>PL in lipid peroxidation inhibition. In the *in vivo* test, the EA treatment increased the average daily weight gain and total antioxidant capacity (T-AOC) in the plasma ($P<0.05$), liver ($P<0.05$), and intestine ($P<0.05$) in oxidatively stressed mice. It increased the SOD activity in the liver ($P<0.05$) and intestine ($P<0.05$), and the GPx activity in the intestine ($P<0.05$). EA treatment decreased the MDA content in the plasma ($P<0.05$), liver ($P<0.05$), and intestine ($P<0.05$) and the mRNA expressions of the pro-inflammatory factors, TNF-α ($P<0.05$), IFN-γ ($P<0.05$) and IL-6 ($P<0.05$). PL increased the SOD activity ($P<0.05$) and GPx activity ($P<0.05$) in the intestine and decreased the MDA content in the intestine ($P<0.05$) and the mRNA expressions of TNF-α ($P<0.05$) and IL-6 ($P<0.05$) in the intestine. PG increased the SOD activity ($P<0.05$) and GSH-Px activity ($P<0.05$) in the intestine and decreased the MDA content in the intestine ($P<0.05$) and IL-6 mRNA expression in the intestine ($P<0.05$) [220].
Gallocatechin, gallocatechin-(4-8)-catechin, gallocatechin-(4-8)-gallocatechin and catechin-(4-8)-gallocatechin	• The prodelphinidin dimers (Gallocatechin-(4-8)-catechin, catechin-(4-8)-gallocatechin and Gallocatechin-(4-8)-gallocatechin) were found potent ABTS$^{\bullet+}$ radical scavengers (with Trolox equivalent antioxidant capacity of 3.56 ± 0.11, 3.50 ± 0.04 and 3.36 ± 0.03) in the aqueous phase, being much more effective than the gallocatechin monomer (2.20 ± 0.08). However, in the lipid phase, only one of the dimers (gallocatechin-(4-8)-catechin) was significantly more effective (IC_{50}= 26.2 ± 0.9) than the monomer (IC_{50}= 38.4 ± 1.1) in the inhibition of lipid peroxidation of phosphatidylcholine vesicles [218].
***Rumex nervosus* leaves**	
Extracts	Methanol extract of Yemeni *Rumex nervosus* • Significant DPPH$^{\bullet}$ radical scavenging activity (IC_{50} = 450 ± 14.3) compared to standard reference, ascorbic acid (IC_{50} = 320 ± 12.0) [243]. Crude methanol extract of Yemeni *Rumex nervosus*, and its sub fractions (ethyl acetate, methanolic, *n*-hexane and chloroform) • The lowest concentrations showing more than 50% DPPH$^{\bullet}$ radical scavenging activity are: 10 μg/ml of ethyl acetate and methanol subfractions with 80.7% and 60,8% comparing to ascorbic acid (91.34% at 10 μg/ml), followed by 20 μg/ml of the crude methanolic extract (53.5%) comparing to ascorbic acid (91.59% at 20 μg/ml) and 40 μg/ml of n-hexane and chloroform fractions with 54.9% and 55.1%, respectively comparing to ascorbic acid (92.59 % at 40 μg/ml) [245]. Ethiopian *R. nervosus* leaves ethyl acetate extract • DPPH$^{\bullet}$ scavenging activity with EC_{50} = 90.23 ± 1.49 mg/L and ABTS$^{\bullet+}$ scavenging activity with EC_{50} = 87.45 ± 1.11 mg/L compared to reference substance BHT with EC_{50} = 1108.47 ± 162.13 mg/L and 62.02 ± 4.43 mg/L, respectively. The $O_2^{\bullet-}$ scavenging activity was (EC_{50} = 33.42 ± 1.45 mg/L). The extract also exhibited FRAP with EC_{50} =13.77 ± 0.27 mg/L compared to BHT with EC_{50} value of 52.40 ± 5.36 μM and Fe2+ chelating activity with EC_{50} = 578.91 ± 20.87 mg/L compared to EDTA with EC_{50} of 0.52±0.07 mg/L [244].
Oil (containing the methyl esters of palmitoleic acid (28.35%), palmitic acid, (25. 37%) and stearic acid (20.25%) as the major components)	• DPPH$^{\bullet}$ radical scavenging activity (93.558% ± 0.4635 at the concentration of 60μg/ml) approaching that of the standard reference ascorbic acid (94.47%) at the same concentration 60μg/ml [245].

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Table S1: *(Continued)*

Raw materials, extracts, and active chemical constituents	Antioxidant mechanisms of action
Thymus laevigatus **Vahl. leaves**	
Methanolic and dichloromethane extracts of Yemeni *T. laevigatus* leaves collected from Haggah, North Yemen	• DPPH• scavenging activity of methanolic and dichloromethane extracts are IC_{50} = 14.9 μg/mL and 28.0 μg/mL, respectively comparing to reference drug ascorbic acid (14.7μg/mL) [252].
Essential oil extracted from Yemeni *T. laevigatus* leaves collected from Sana'a	• DPPH• radical scavenging activity (0.08997% ± 1.51, 0.0767 % ± 1.11 , and 0.0616% ± 1.23 at 1.00, 0.5, and 0.25 mg/ l, respectively), compared to the reference substance ascorbic acid (0.0378%, 0.0352%, and 0.0183% at 1.00, 0.5, and 0.25 mg mL) [253].
Essential oil obtained from the aerial part of Pakistani *T. serpyllum* (synonym = *T. laevigatus*) and its major component, carvacrol	• DPPH• scavenging activity and inhibition of linoleic acid peroxidation of carvacrol were weaker (IC_{50} = 88.8 ± 2.8 and 49.6% ± 1.7, respectively) than that of the essential oil itself (IC_{50} = 34.8 ± 1.9 and 84.2% ± 3.7, respectively) compared with the reference substance BHT (IC_{50} = 15.4 ± 0.4 and 90.9% ± 2.7, respectively) [254].
Thymol	• DPPH• scavenging activity with IC_{50} = 22.4 ± 0.8 and the inhibition of linoleic acid peroxidation was 87.6% ± 3.2 compared with the reference substance BHT (IC_{50} = 15.4 ± 0.4 and 90.9% ± 2.7, respectively) [254].